

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

**In re application of:**

William J. Curatolo et al.

**Application No.** 09/770,562

**Filed:** January 26, 2001

**Confirmation No.** 8513

**For:** SOLID PHARMACEUTICAL DISPERSIONS  
WITH ENHANCED BIOAVAILABILITY

**Examiner:** Blessing M. Fubara

**Art Unit:** 1613

**Attorney Reference No.** 8191-87018-01

**FILED VIA EFS**  
**ON November 28, 2011**

FILED VIA ELECTRONIC FILING SYSTEM  
COMMISSIONER FOR PATENTS

**DECLARATION OF ANN W. NEWMAN UNDER 37 C.F.R. § 1.132**

ANN W. NEWMAN, being duly sworn does hereby declare and affirm the following:

1. That she received a B.S. in Chemistry and Medical Technology from SUNY Fredonia in 1983 and a Ph. D. in Inorganic Chemistry from the University of Connecticut in 1988.
2. That she is employed as a Pharmaceutical Consultant at Seventh Street Development Group from 2009-present; that she previously worked as Vice President, R&D at Aptuit from 2007-2008; that she previously worked as Vice President, Materials Science at SSCI, Inc. from 1998-2007; and that she worked at Bristol-Myers Squibb as a Principal Scientist in 1998, a Senior Research Investigator II from 1994–1998, a Senior Research Investigator I from 1990–1994 and a Research Investigator from 1988-1990. (*Curriculum Vitae* attached as Exhibit A.)
3. That she has over 20 years' experience in solid form characterization, screening, selection, scale-up, quantitation, and problem solving for large and small pharmaceutical companies including amorphous materials and amorphous solid dispersions. That she has over 20 publications, presentations, and webcasts dealing specifically with amorphous materials and amorphous solid dispersions.
4. That she has been asked by Bend Research, Inc. to provide her independent expert opinion on spray-drying technology and the production of amorphous and/or crystalline dispersions using the same, and on the state of the art of spray-drying technology *circa* 1997 in regard to certain issues raised in the Decision by the Board of Patent Appeals and Interferences (BPAI), dated March 29, 2011, and the Office

Action dated August 26, 2011. That she will be compensated for her time, at her normal consulting rate, but that her compensation is not conditioned on her rendering any particular opinion.

5. That she has read and understands the above-identified patent application, including the pending claims, and has also read the Board of Patent Appeals and Interferences Decision dated March 29, 2011, the Office Action dated August 26, 2011, and all of the references cited therein.

6. That she understands that the claims as pending all include a spray dried solid dispersion consisting of water-soluble drug and hydroxypropyl methylcellulose acetate succinate (HPMCAS), the drug being molecularly dispersed and amorphous in the dispersion. That is, the drug is completely amorphous, not crystalline, in the spray dried solid dispersion.

7. That, in summary, she believes, based on her knowledge of spray drying and materials science and her knowledge of the state of spray drying spray-dried dispersions in or about 1997, that:

- That spray dried solid dispersions are not necessarily completely amorphous but instead may be all crystalline, partially crystalline or all amorphous depending upon the spray-drying parameters and conditions used when spray drying the solid dispersion.
- That the references the Examiner cites do not necessarily disclose spray dried solid dispersions that are completely amorphous.
- That the references the Examiner cites do not give any guidance whatsoever as how to make spray dried solid dispersions that are completely amorphous.
- That one of ordinary skill in the art in 1997 would not have had the knowledge to make up for the deficiencies of the disclosures of the cited references and could not have made spray dried solid dispersions that are completely amorphous from reading the cited references.
- That even if one of ordinary skill in the art were to have tried to do so in 1997, there would not have been a reasonable expectation of success at that time.

8. That the references cited by the Examiner do not necessarily indicate that a completely amorphous spray-dried dispersion was made or would be made even though the polymer HPMCAS is disclosed in these references. Specifically:

- Miyajima – EP 0 344 603

That nothing in this reference indicates that Miyajima produced a completely amorphous spray dried solid dispersion. That the Miyajima disclosure to which the Examiner cites - 1-7 parts or 3-5 parts by weight of HPMCAS used per 1 part by weight NZ-105 (and related portions) - does not indicate it made a completely amorphous solid dispersion and no conditions for spray drying are disclosed so one cannot determine whether Miyajima could even have produced a completely

amorphous solid dispersion. That the Miyajima product may include small crystals of crystalline material dispersed in the polymer. That the smaller size would help the dissolution rate and performance, but the performance may not be as good as producing a completely amorphous material. That early dispersion papers talk about decreasing the particle size of the crystalline material and dispersing in a polymer to improve performance, which may be what Miyajima was contemplating in his disclosure.

Additionally, that Examples 1-6 add urea to the formulation. Thus, it is possible that the HCl salt used could form a co-crystal with the other components or possibly break (producing the free base) with the API forming a different salt, co-crystal, or complex that could result in the dissolution and blood level concentration improvements cited in the patent.

That there is insufficient guidance (no guidance) in Miyajima as to the spray drying process conditions to use to make a completely amorphous solid dispersion or to test the Miyajima disclosure to determine whether a completely amorphous material would have resulted.

- Kigoshi EP 0 784 974

That the limited information in this reference does not indicate that Kigoshi produced a completely amorphous spray dried solid dispersion with HPMCAS. That there is insufficient guidance (no guidance) in Kigoshi as to the spray drying process conditions to use to make a completely amorphous solid dispersion or to test the Kigoshi disclosure to determine whether a completely amorphous material would have resulted at least in part because the examples only describe a fluid bed granulator process.

- Hikosaka JP 57-176907

That nothing in this reference indicates that Hikosaka produced a completely amorphous spray dried solid dispersion. That Hikosaka states that the drug is present in "a substantially amorphous state" which indicates that at least a portion of the composition is crystalline. That this likely means that there were some minor peaks in the XRPD patterns shown in the figures for some samples; and that the figures are not of sufficient scale to determine the extent of crystallization and if plotted on a different peak intensity scale (y-axis) that small crystalline peaks would be evident indicating that the materials are not completely amorphous.

That Examples 1-4, besides not being HPMCAS, do not provide any detail on spray drying conditions (nor does the disclosure in general) so reproducing what Hikosaka performed to get samples representative of the powder patterns disclosed in the patent is not possible.

That the Hikosaka HPMCAS examples (Examples 5 and 6) are evaporated, not spray dried.

That since there is insufficient guidance (no guidance) in Hikosaka as to the spray drying process conditions to make its solid dispersion, one of ordinary skill in the art cannot test the Hikosaka disclosure to determine whether a completely amorphous material could have resulted. That the language used in Hikosaka "substantially amorphous" indicates that it was not completely amorphous.

9. That the references cited by the Examiner in the August 26, 2011, Office Action do not give sufficient information to perform a spray drying process to achieve the Applicant's present claimed compositions – particularly producing a completely amorphous composition. That is, spray drying will not produce a completely amorphous solid dispersion regardless of the spray drying conditions used.

10. That based on my knowledge and experience and the state of spray drying technology in August of 1997, I do not believe that the cited references provide sufficient disclosure that one of ordinary skill in the art at that time could have made the claimed spray dried dispersions based on that skilled person's knowledge combined with the disclosures cited by the Examiner. That to do so in August 1997 would not only have been unpredictable, it would have taken extensive experimentation and there would not have been an expectation of success.

11. That the following articles evidence that spray-drying can produce crystalline and/or amorphous materials depending upon the spray drying conditions and process parameters. That is, in reviewing some of the many articles studying variations of spray drying conditions and effects on resulting powders' crystallinity percentages, it is clear that **spray drying does not necessarily result in a completely amorphous solid dispersion but instead, depending on the conditions of the spray drying, the resulting powder may be crystalline, amorphous or a mixture of the two forms.**

- a. Chiou, "Partial Crystallization Behavior during Spray Drying: Simulations and Experiments" *Drying Technology*, 26: pp. 27-38 (2008). (Exhibit B.)

That Chiou investigates varying spray drying conditions, such as air inlet temperature, and its effects on the crystallization of the resulting product. For example, Chiou states that *"manipulation of the operating conditions in a dryer, and the properties of the feed, may allow the drying process itself to either minimize or maximize the degree of crystallinity in the products, rather than allow an amorphous material to crystallize in storage."* (Pp. 27-28.) See for Example,



Table 3 showing variation in spray drying conditions such as inlet air temperature, aspirator rate, pump rate, nozzle flow rate, and inlet concentration of material in solution where products were produced as 100% crystalline, 100% amorphous and various mixtures of crystalline and amorphous.

That Chiou also mentions (more than 10 years after Applicant filed its application) that his experimental model provided "*insights into the complex interactions involved in spray drying and crystallization. Larger changes in crystallization behavior can be caused by modifying the operating temperatures, with greater crystallization being given at higher temperatures, together with lowering the concentration of the feed material to give higher humidities in the drying air to give partial crystallization on particle surfaces.*" (P. 36.) That Chiou also states: "*The simulation tool therefore appears to be useful for predicting trends in the partial or complete crystallization behavior of spray-dried products as the feed composition or the operating conditions in the spray dryer are changed.*"

- b. Chidavaenzi, "The use of thermal techniques to assess the impact of feed concentration on the amorphous content and polymorphic forms present in spray dried lactose" *International Journal of Pharmaceutics*, 159, pp. 67-74 (1997). (Exhibit C.)

That Chidavaenzi determines that variation of feed concentration during spray drying leads to products with different percentage amorphous contents and different proportions of crystalline forms. See, for example, the Abstract, p. 70, or Table 2 on p 72. That Chidavaenzi also notes that other spray drying conditions such as atomization pressure in a spray nozzle and temperature of the feed and nozzle temperature will vary the percentage of crystalline/amorphous materials in the resulting product. (Pp. 70-71.)

- c. That further example evidence that spray drying does not necessarily result in amorphous dispersions but instead, depending on the conditions of the spray drying, the resulting powder may be crystalline, amorphous or a mixture of the two states, are as follows:
  - i. That the following illustrate that feedstock solution preparation and spray drying conditions of the same API with a polymer can result in crystalline resulting materials and that developing appropriate spray drying conditions is critical to producing amorphous materials. Corrigan, "Physicochemical Properties of Spray Dried Drugs: Phenobarbitone and Hydroflumethiazide" *Drug Dev Ind Pharm*, Vol. 9, pp. 1-20 (1983) (Exhibit D) and Corrigan, "Physicochemical Properties of Indomethacin and

Related Compounds Co-spray Dried with Polyvinylpyrrolidone" *Drug Dev Ind Pharm*, Vol. 11, pp. 677-695 (1985) (Exhibit E).


ii. See also:

- Corrigan et al., "Predicting the physical state of spray dried compositions: salbutamol sulphate/lactose and salbutamol sulphate/polyethylene glycol co-spray dried systems," *International Journal of Pharmaceutics*, Vol. 273, pp. 171-182 (2004) (Exhibit F).
- Appel, Leah, "Amorphous Solid Dispersions," *Green Ridge Consulting*, PowerPoint Slide Presentation (July 30, 2009) (Exhibit G).
- Pastilha et al., "Hovione Expands its Particle Design Technologies with the Latest CGMP Spray Dryer Facility," *Particle Design Technology*, 4 pages (2004) (Exhibit H).

12. That she has reviewed the present application and believes there to be sufficient direction, guidance and examples in the specification such that one of ordinary skill in the art in August of 1997 could have made a spray dried solid dispersion consisting of a sparingly water-soluble drug and HPMCAS, the drug being molecularly dispersed and amorphous in the dispersion, having a drug:polymer weight ratio between 1:0.4 and 1:20, and the dispersion being a homogeneous solid solution of said drug in the HPMCAS with little or no experimentation, through reading Applicant's disclosure. That she has found particular guidance for making the same in the specification at, for example, p. 15, lines 16-19, p. 15, line 25 to p. 16, line 26, p. 21, line 23 to p. 24, line 9 and examples 15, 23, 1, 25, 26, 28 and 30.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Executed at the place and date opposite the signature below.

  
\_\_\_\_\_  
Ann W. Newman

At Lafayette, IN  
(City and State)  
on this 23 day of November 2011.



**Profile** Senior pharmaceutical scientist with demonstrated scientific and leadership expertise in the pharmaceutical industry based on over 20 years of large pharma and contract research experience. Strong knowledge base in pharmaceutical sciences including problem-solving, drug development, solid state chemistry (polymorphs, salts, cocrystals, amorphous, dispersions), crystallization, physical characterization (active pharmaceutical ingredients (API), excipients, and drug products), preformulation studies, process-induced transformations, current Good Manufacturing Practices (cGMP), regulatory, and intellectual property (IP).

**Education** Ph.D., Inorganic Chemistry, University of Connecticut, Storrs, CT 1988  
 B.S., Chemistry and Medical Technology, SUNY at Fredonia, Fredonia, NY 1983

## Professional

**Experience** **Seventh Street Development**, Lafayette, IN Pharmaceutical Consultant 2009-present

- Provided consulting, training, and webcast services on solid-state pharmaceuticals and pharmaceutical development.
- Projects included solid form characterization and quantitation, screening (polymorphs, salts, cocrystals, amorphous dispersions), crystallization of Phase I materials, process induced transformations, compilation of information for intellectual property documentation

**Aptuit**, West Lafayette, IN Vice President, R&D 2007–2008  
 (Aptuit purchased SSCI in Oct. 2006)

- Developed and implemented new global research and development function within company covering both scientific and clinical operations over six sites.
- Responsible for overseeing system with over 70 R&D projects and over 80 people participating in R&D projects. Scientific areas included API, preclinical (toxicology, safety, pharmacokinetics), formulation, solids, analytical, clinical packaging, and regulatory.
- Chaired the Technical Development Committee consisting of scientific leaders of the company.
- Worked with Scientific Advisory Board and Technical Development Committee to perpetuate innovation within the company.
- Acted as a company resource for scientific projects, new offerings, and new technologies.
- Codeveloped initial Aptuit INDiGO™ fast to IND offering based on internal R&D project.

**SSCI, Inc.**, West Lafayette, IN Vice President, Materials Science 1998–2007

- Played an important role in the rapid growth of the company, including staffing, systems design and implementation, client development, technical output, and scientific innovation.
- Interfaced with clients on scientific and regulatory issues as well as client problems.
- Planned and supervised scientific projects including solid form screens and selection (polymorphs, salts, cocrystals, amorphous, amorphous solid dispersions), physical characterization, crystallization, crystal form quantitation, and process chemistry.
- Managed twenty scientists working on client and R&D projects.
- Provided short courses and training for employees and client companies.
- Represented company at conferences and exhibitions.

<b>Bristol-Myers Squibb</b> , New Brunswick, NJ	Principal Scientist	1998
	Senior Research Investigator II	1994–1998
	Senior Research Investigator I	1990–1994
	Research Investigator	1988–1990

- Responsible for physical characterization function in the Bristol-Myers Squibb Pharmaceutical Research Institute, including support of crystal form/salt selection, bulk drug scale-up, and formulation development. Scope included late Drug Discovery through Phase IV, as well as marketed products when needed.
- Provided characterization assistance and expertise to other divisions (Legal, Technical Operations, Apothecon, Bristol-Myers Products, Convatec) when needed.
- Provided written documentation on physical characterization of selected crystal form for IND and NDA filings and summary reports for crystal form/salt selection.
- Represented group and inter and intra-departmental meetings, as well as external conferences.

<b>Academic Experience</b>	<b>Purdue University</b> , West Lafayette, IN	Adjunct Professor/Lecturer	2000–present
		Industrial and Physical Pharmacy	

- Served on doctoral graduate student committees and assisted with doctoral projects
- Guest lecturer in undergraduate and graduate courses (IPPH 690 and IPPH 100)
- Limited term lecturer for IPPH 362 Basic Pharmaceutics: Solution Dosage forms 2011

<b>Rutgers University</b> , New Brunswick, NJ	Outside Examiner	1992–1997
---	------------------	-----------

- Served on doctoral graduate student committees

## Training

<b>Experience</b>	<b>Seventh Street Development Group</b> , Lafayette, IN	
	• Seventh Street Development Group <u>Live Webcasts</u>	2009–2011
	• Seventh Street Development Group <u>On Demand Webcasts</u>	2009–2011
	• ACS <u>Webcast Series</u> “Polymorphism in Organic/Pharmaceutical Systems”	2009–2010
	• ACS <u>On Demand Webcast Course</u> “Solid State Characterization of Organic Compounds”	2011
	• On-site Short Course “Solid State Characterization of Pharmaceutical Solids”	2010

**SSCI**, West Lafayette, IN

- Polymorphs and Solvates of Drugs Short Course 1997–2004
- Process Analytical Technology (PAT) Short Course 2003
- Particle Formation and Characterization Short Course 2000

**Bristol-Myers Squibb**, New Brunswick, NJ

- Physical Characterization of Pharmaceutical Solids Training 1996–1998
- Computational Methods in Pharmaceutical Characterization 1997
- Particle Size Methods 1994
- Scientists in the Classroom, Lawrence School District 1994

**Publications** Author on over 40 technical publications, presenter/collaborator for over 75 presentations, and presenter for over 40 webcasts.

**Affiliations** American Chemical Society (ACS), American Association of Pharmaceutical Scientists (AAPS), Special Editor for Journal Pharmaceutical Sciences Special Issue for Steve Byrn, 2011 and 2012 Planning Committee for June Land O’Lakes Conference, Cambridge Who’s Who.

## Publications

"X-ray Powder Diffraction in Solid Form Screening and Selection" A. Newman. *Amer. Pharm. Rev.* **2011**, Sept/Oct, 44-51.

"A Solid-State Approach to Enable Early Development Compounds: Selection and Animal Bioavailability Studies of an Itraconazole Amorphous Solid Dispersion" D. Engers, J. Teng, J. Jimenez-Novoa, P. Gent, S. Hossack, C. Campbell, J. Thomson, I. Ivanisevic, A. Templeton, S. Byrn, A. Newman. *J. Pharm. Sci.*, **2010**, 99(9), 3901-3922.

"Pharmaceutical Cocrystals and Their Physicochemical Properties" N. Schultheiss, A. Newman. *Cryst. Growth Des.*, **2009**, 9(6), 2950-2967.

"Characterization of API : Polymer Mixtures Using X-ray Powder Diffraction" A. Newman, D. Engers, S. Bates, I. Ivanisevic, R. C. Kelly, G. Zografi, *J. Pharm. Sci.*, **2008**, 97(11), 4840-4856.

"Minireview: Characterization of the "Hygroscopic" Properties of Active Pharmaceutical Ingredients" A. W. Newman, S. M. Reutzel-Edens, G. Zografi, *J. Pharm. Sci.*, **2008**, 97(3), 1047-1059.

"Salt Cocrystal Form Selection" A. W. Newman, S. L. Childs, B. A. Cowans, in *Preclinical Development Handbook*, John Wiley and Sons, Hoboken, **2008**, 455-481.

"Assessment of Defects and Amorphous Structure Produced in Raffinose Pentahydrate upon Dehydration" S. Bates, R. Kelly, P. Schields, I. Ivanesevic, G. Zografi, A. W. Newman, *J. Pharm. Sci.*, **2007**, 96(5), 1418-1433.

"Relationship of Triboelectric Charging and Dielectric Properties of Pharmaceutically-Relevant Mixtures" D.A. Engers, M.N. Fricke, A.W. Newman, and K.R. Morris, *J. Electrostat.*, **2007**, 65, 571-581.

"Thermal Microscopy" I. M. Vitez, A. W. Newman, in *Thermal Analysis of Pharmaceuticals*, CRC Press, Boca Raton, **2007**, 221-264.

"PAT – Process Understanding and Control of Active Pharmaceutical Ingredients" S. R. Byrn, J. K. Liang, S. Bates, Ann W. Newman, *Journal of PAT*, **2006**, 3(6), 14-19.

"Analysis of Amorphous and Nanocrystalline Solids from Their X Ray Diffraction Patterns" S. Bates, G. Zografi, D. Engers, K. Morris, K. Crowley, A. Newman, *Pharm. Res.*, **2006**, 23(10), 2333-2349.

"Triboelectrification of Pharmaceutically-Relevant Powders During Low-Shear Tumble Blending" D. A. Engers, M. N. Fricke, R. P. Storey, A. W. Newman, and K. R. Morris, *J. Electrostat.*, **2006**, 64, 826-835.

"The Physical Characterization of Hygroscopicity in Pharmaceutical Solids" S. M. Reutzel-Edens and A. W. Newman, in *Polymorphism*, Wiley-VCH, Weinheim, **2006**, 235-258.

"Solid-state Analysis of the Active Pharmaceutical Ingredient in Drug Products", A. W. Newman, S. R. Byrn, *Drug Discovery Today*, **2003**, 8(19), 898-905.

"Form Selection of Pharmaceutical Compounds", A. W. Newman and G. P. Stahly, in *Handbook of Pharmaceutical Analysis*, Marcel Dekker, New York, **2002**, vol. 117, 1-57.

"Chemical Reactivity in Solid-State Pharmaceutics", S. R. Byrn, W. Xu, A. W. Newman, *Adv. Drug Delivery Rev.*, **2001**, 48(1), 115-136.

"The Role of Powder X-Ray Diffraction as a Powerful Tool in Characterization of Various Hydrates of a Drug Substance", M. Davidovich, R. Mueller, K. Raghaven, S. Ranadive, I. Vitez, B. Sarsfield, J. DiMarco, J. Gougoutas, A. Newman, *Amer. Pharm. Rev.*, **2001**, 4(1), 53-60.

"Sorbitol", A. W. Newman, I. M. Vitez, R. L. Mueller, C. Kiesnowski, M. Davidovich, W. P. Findlay, *Analytical Profiles of Drug Substances and Excipients*, Academic Press, New York, **1999**, vol. 26, 459-502.

"The Evolution of Hot Stage Microscopy to Aid Solid State Characterizations of Pharmaceutical Solids", I. M. Vitez, A. W. Newman, M. Davidovich, C. Kiesnowski, *Thermochimica Acta*, **1998**, 324, 187-196.

"Physical Characterization of the Polymorphic Variations of Magnesium Stearate and Magnesium Palmitate Hydrate Species", S. A. Sharpe, M. Celik, A. W. Newman, H. G. Brittain, *Struct. Chem.*, **1997**, 8, 73-84.

"Quantitation of Pseudopolymorphism in Cefepime.2HCl by Diffuse Reflectance IR and Powder X-ray Diffraction Techniques", D.E. Bugay, A. W. Newman, W. P. Findlay, *J. Pharm. and Biom. Anal.*, **1996**, 15, 49-61.

"Starches and Starch Derivatives", A. W. Newman, I. M. Vitez, C. Kiesnowski, R. Mueller, in *Encyclopedia of Pharmaceutical Technology*, Marcel Dekker, New York, **1996**, vol 14, 223-248.

"Starch", A. W. Newman, I. M. Vitez, C. Kiesnowski, R. Mueller, D. E. Bugay, W. P. Findlay, C. Rodriguez, in *Analytical Profiles of Drug Substances and Excipients*, Academic Press, New York, **1996**, vol 24, 523-578.

"Particle Morphology: Optical and Electron Microscopies", A. W. Newman and H. G. Brittain, in *Physical Characterization of Pharmaceutical Solids*, H. G. Brittain, Ed., Marcel Dekker, New York, **1995**, 127-156.

"Micromeritics", A. W. Newman, in *Physical Characterization of Pharmaceutical Solids*, H. G. Brittain, Ed., Marcel Dekker, New York, **1995**, pp. 253-280.

"Talc", A. W. Newman, I. M. Vitez, P. Cortina, G. Young, J. DeVincentis, D. E. Bugay, T. Patel, *Analytical Profiles of Drug Substances and Excipients*, Academic Press, New York, **1994**, vol 23, 511-542.

"Characterization of Humidity-Dependent Changes in Crystal Properties of a New HMG-CoA Reductase Inhibitor in Support of its Dosage Form Development", K. R. Morris, D. E. Bugay, A. W. Newman, S. A. Ranadive, A. K. Singh, M. Szyper, S. A. Varia, H. G. Brittain, A. T. M. Serajuddin, *Int. J. Pharm.* **1994**, 108, 195-206.

"An Integrated Approach to the Selection of Optimal Salt Form for a New Drug Candidate", K. R. Morris, M. G. Fakes, A. B. Thakur, A. W. Newman, A. K. Singh, J. J. Venit, C. J. Spagnuolo, A. T. M. Serajuddin, *Int. J. Pharm.* **1994**, 105, 209-217.

"Factors Affecting Differences in Film Thickness of Beads Coated in Fluidized Bed Units", R. Wesdyk, Y. M. Joshi, J. DeVincentis, A. Newman, N. B. Jain, *Int. J. Pharm.* **1993**, 93, 101-109.

"Physical Interactions of Magnesium Stearate with Starch-Derived Disintegrants and Their Effects on Capsule and Tablet Dissolution", D. S. Desai, B. A Rubitski, S. A. Varia, A. W. Newman, *Int. J. Pharm.* **1993**, 91, 217-226.

"Changes in Material Properties Accompanying the NF Identity Test for Microcrystalline Cellulose", H. G. Brittain, G. Lewen, A. W. Newman, K. Fiorelli, S. Bogdanowich, *Pharm. Res.* **1993**, 10(1), 61-67.

"Titanium Dioxide", H. G. Brittain, G. Barbera, J. DeVincentis, A. W. Newman, *Analytical Profiles of Drug Substances and Excipients*, Academic Press, New York, **1992**, vol 21, pp. 659-691.

"Physical Characterization of Pharmaceutical Solids", H. G. Brittain, S. J. Bogdanowich, D. E. Bugay, J. DeVincentis, G. Lewen, A. W. Newman, *Pharm. Res.* **1991**, 8(8), 963-973.

"Anhydrous Lactose", H. G. Brittain, S. J. Bogdanowich, D. E. Bugay, J. DeVincentis, G. Lewen, A. W. Newman, *Analytical Profiles of Drug Substances and Excipients*, Academic Press, New York, **1991**, vol 20, 369-398.

"The Effect of Size and Mass on Film Thickness of Beads Coated in Fluidized Bed Equipment", R. Wesdyk, N. Jain, Y. M. Yoshi, K. Morris, A. Newman, *Int. J. Pharm.* **1990**, 65, 69-76.

"Relationship Between the Physical and Mechanical Properties of Wet Granulated Microcrystalline Cellulose Following Drying", M. Chatrath, J. N. Staniforth, A. Winiecki Newman, H. G. Brittain, *J. Pharm. Pharmacology* **1990**, 42, 80P.

"Electrocatalytic Reactions in Organized Assemblies. 6. Electrochemical and Spectroscopic Studies of Catalytic Clay Micelle Electrodes", C. Shi, J. F. Rusling, Z. Wang, W. S. Willis, A. M. Winiecki, S. L. Suib, *Langmuir* **1989**, 5(3), 650-660.

"Chemical Stability of Aluminophosphate Molecular Sieves During Hydrochloric Acid Treatment", A. M. Winiecki, S. L. Suib, *Langmuir* **1989**, 5(2), 333-338.

"X-Ray Photoelectron Spectroscopy Investigations of Zeolites", A. M. Winiecki, S. L. Suib, M. L. Occelli, *Langmuir* **1988**, 4(3), 512-518.

"Surface Chemical States of Aluminophosphate and Silicoaluminophosphate Molecular Sieves", S. L. Suib, A. M. Winiecki, A. Kostapapas, *Langmuir* **1987**, 3(4), 483-488.

"Surface States of Aluminophosphate and Zeolite Molecular Sieves", S. L. Suib, A. M. Winiecki, A. Kostapapas, *Stud. Surf. Sci. Catal. Vol. 28*, Y. Murakawa, A. Iijima, J. W. Ward, Eds., Elsevier, Amsterdam, **1986**, 409-415.

"Photoassisted Catalysis in Organized Media: Olefin Isomerization via Photolysis of Metal Carbonyls in Zeolites", S. L. Suib, A. Kostapapas, K. C. McMahon, J. C. Baxter, A. M. Winiecki, *Inorg. Chem.* **1985**, 24, 858-863.

#### **Invited Presentations**

"Solid Form Screening and Selection during Development" A. Newman, invited talk at CrystEngComm Pharmaceutical Polymorphism Symposium, London, UK, November 2011.

"Solid State Chemistry of Biopharmaceuticals: Fundamental Issues and Study Approaches" A. Newman, S. Byrn, S. Bogdanowich-Knipp, H. Zhang, R. Von Dreele, invited talk at Asian Arden House, Seoul, South Korea, June 2011.

"An Overview of Solid Form Screening during Drug Development" A. Newman, invited talk at 10th Pharmaceutical Powder X-Ray Diffraction Symposium (PPXRD-10), Lyons France, May 2011.

"Amorphous Basics" A. Newman, invited talk at the Understanding Pharmaceutical Amorphous Materials Workshop, 10th Pharmaceutical Powder Diffraction X-Ray Diffraction Symposium (PPXRD-10), Lyons France, May 2011.

"Making Amorphous API" A. Newman, invited talk at the Understanding Pharmaceutical Amorphous Materials Workshop, 10th Pharmaceutical Powder Diffraction X-Ray Diffraction Symposium (PPXRD-10), Lyons France, May 2011.

"Using Thermal Techniques for Amorphous Materials" A. Newman, invited talk at the Understanding Pharmaceutical Amorphous Materials Workshop, 10th Pharmaceutical Powder Diffraction X-Ray Diffraction Symposium (PPXRD-10), Lyons France, May 2011.

"Case Study: Physical Chemical Properties-Changes During Development" A. Newman, invited talk at June Land O'Lakes Conference, 52<sup>nd</sup> Annual International Industrial Pharmaceutical Research and Development Conference on Science-Driven Drug Product Development Strategies to Achieve Proof of Concept, Merrimac, June 2010.

"Drug Product Characterization: What Form Do I Have?" A. Newman, invited talk at 9th Pharmaceutical Powder Diffraction X-Ray Diffraction Symposium (PPXRD-9), Hilton Head, February 2010.

"Amorphous and Amorphous Dispersion Basics", A. Newman, invited talk at the Understanding Pharmaceutical Amorphous Materials Workshop, 9th Pharmaceutical Powder Diffraction X-Ray Diffraction Symposium (PPXRD-9), Hilton Head, February 2010.

"Role of Solid Forms in Lifecycle Management" A. Newman and J. Hastedt, invited workshop at Pharma IQ's 8<sup>th</sup> Annual Polymorphism and Crystallization Scientific Forum, Philadelphia, October 2009.

"Form Selection to Improve Solubility" A. Newman, invited talk at Pharma IQ's 4<sup>th</sup> Annual Improving Solubility Conference 2008, London, June 2008.

"Comprehensive Approach to Form Screening" A. W. Newman, invited talk at Polymorphism and Crystallization Scientific Forum, Philadelphia, September 2005.

"Amorphous and Disordered Pharmaceutical Materials" S. Bates and A.W. Newman, invited workshop at Polymorphism and Crystallization Scientific Forum, Philadelphia, September 2005.

"Process-Induced Transformations" A. W. Newman, invited presentation at Polymorphism, Crystallization and Salt Selection Conference, Washington, DC, February 2005.

"Cocrystallization as a Feasible Method of Solid Form Screening" S. Childs and A. W. Newman, invited workshop at Polymorphism, Crystallization and Salt Selection Conference, Washington, DC, February 2005.

"Process Analytical Technology (PAT): Achieving Mechanistic Understanding through Solid-State Chemistry" S. R. Byrn and A. W. Newman, invited workshop at Polymorphism, Crystallization and Salt Selection Conference, Washington, DC, February 2005.

"Analysis of Short-range Order in X-ray Amorphous Indomethacin Using X-ray Powder Diffraction and Pair-Wise Distribution Functions" A. W. Newman, S. Bates, G. Zografi, K. Crowley, invited presentation at Preformulation/Formulation Strategies Conference, Philadelphia, February 2005.

"Trouble Shooting Phase Transitions During Processing", A. W. Newman, invited presentation at Polymorphism and Crystallization Forum, Princeton, April 2004.

"An Overview of Form Selection", Form Selection for Pharmaceutical Systems Workshop, A. W. Newman, invited presentation at Polymorphism and Crystallization Forum, Princeton, April 2004.

"A Tiered Approach to Salt and Cocrystal Selection", A. W. Newman, invited presentation at Salt Selection and Formulation /Preformulation Strategies, Philadelphia, March 2004.

"Commonly Used Techniques to Characterize Phase Transitions During Processing", A. W. Newman, invited presentation at AAPS Annual Meeting, Toronto, November 2002.

"SSCI and MSI Joint Venture", A. W. Newman, invited talk at Molecular Simulations Inc. Pharmaceutical Development Consortium Meeting, March 1999.



"The Effect of Particle Size at Various Stages of Pharmaceutical Manufacturing: Using Traditional and Non-Traditional Techniques", A. W. Newman, J. DeVincentis, G. Lewen, D. Bergman, K. Fiorelli, S. J. Bogdanowich invited talk at Fine Particle Society 23rd Annual Meeting, July 1992.

### **Professional Presentations**

"Screening and Animal Bioavailability Studies on Itraconazole Amorphous Dispersions" D. Engers, J. Teng, J. Jimenez-Novoa, P. Gent, S. Hossack, C. Campbell, J. Thomson, I. Ivanisevic, A. Templeton, S. Byrn, A. W. Newman at AAPS, Atlanta, November 2008.

"Computational Studies of API:Polymer Mixtures From X-ray Powder Diffraction Data" S. Bates, I. Ivanisevic, P. Chen, D. Engers, R. Kelly, A. Newman, G. Zografi at 6th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Barcelona, Spain, April 2008.

"Characterization of API:Polymer Mixtures using X-ray Powder Diffraction" S. Bates, R. Kelly, D. Engers, G. Zografi, A. Newman at AAPS, San Diego, November 2007.

"Analysis of Process Induced Defects in Pharmaceutical Solids" S. Bates, P. Schields, I. Ivanisevic, R. Kelly, G. Zografi, A. W. Newman at AAPS Annual Meeting, San Antonio, October 2006.

"In-situ Monitoring of a Drying Process for a Complex Hydrate API using Raman Spectroscopy" J. K. Liang, A. W. Newman, J. Stults, V. Smolenskaya at AAPS Annual Meeting, Nashville, November 2005.

"Relationship Between Triboelectric Charge and Dielectric Response in Binary Mixtures Containing Metal Stearates" D. A. Engers, M. W. Nowling, A. W. Newman, and K. R. Morris at Purdue-Michigan Program for the Study of Supramolecular Assemblies and Solid-State Properties, West Lafayette, IN, September 2005.

"Pair-Distribution Functions: Probing the Evolution of Microstructure in Amorphous Pharmaceutical Materials" D. A. Engers, K. R. Morris, G. Zografi, A. W. Newman, S. Bates at Midwest Organic Solid State Chemistry Symposium XVI, West Lafayette, June 2005.

"Polymorph and Crystallization Studies of dOTC", A. W. Newman, M. C. Andres, G. P. Stahly, A. Cimpola at AAPS Annual Meeting, Toronto, November 2002.

"Quantitation of dOTC Form A in Drug Product Using X-Ray Powder Diffraction", A. W. Newman, M. C. Andres, A. Cimpola at AAPS Annual Meeting, Toronto, November 2002.

"Unsolvated Enantiotropic Polymorphs of Loperamide Hydrochloride", A. W. Newman, M. C. Andres, G. P. Stahly, L. Ohannessian, A. Adair at AAPS Annual Meeting, Toronto, November 2002.

"Quantitation of Two Polymorphic Forms Using Rietveld Analysis, Synchrotron X-Ray Powder Diffraction, and Traditional X-Ray Powder Diffraction," A. W. Newman, H. Morrison, M. Andres, G. Stahly, A. Thomas, P. Stephens at First Annual International Workshop on Physical Characterization of Pharmaceutical Solids, Lancaster, PA, September, 2000.

"The Role of Powder X-ray Diffraction as a Powerful Tool in the Characterization of Various Hydrates of a Drug Substance," M. Davidovich, J. DiMarco, J. Gougoutas, R. Mueller, A. Newman, K. Raghavan, S. Ranadive, I. Vitez, B. Sarsfield at First Annual International Workshop on Physical Characterization of Pharmaceutical Solids, Lancaster, PA, September, 2000.

"Use of Variable Temperature Assays to Study the Physical Properties of a Solid Bulk Drug Substance," I. M. Vitez, M. Davidovich, W. P. Findlay, M. Galella, G. McGeorge, R. L. Mueller, A. W. Newman, B. Sarsfield at the 39<sup>th</sup> Eastern Analytical Symposium, Somerset, November, 1999.

"Quantitation of Two Polymorphic Forms Using X-Ray Powder Diffraction and Rietveld Analysis", A. W. Newman, P. Stephens, H. G. Morrison, M. C. Andres, A. S. Thomas, G. P. Stahly at AAPS Annual Meeting, November 1999.

"Quantitation of Amorphous Material in Micronized Levalbuterol Sulfate", Paul McGlynn, Martin P. Redmon, Stephen A. Wald, Henry G. Morrison, Ann W. Newman, Brenton W. Russell, G. Patrick Stahly, David E. Bugay, Li Li-Bovet, and Agustin F. Venero at AAPS Annual Meeting, November 1999.

"Quantitation of Two Polymorphic Forms Using Rietveld Analysis, Synchrotron X-Ray Powder Diffraction, and Traditional X-Ray Powder Diffraction", A. W. Newman, P. W. Stephens, M. C. Andres, G. P. Stahly, H. G. Morrison, and A. S. Thomas at ICDD Pharmaceutical Symposium, September 1999.

"Crystal Form Quantitation Using Rietveld Analysis", A. W. Newman, M. C. Andres, M. C. Wahle at Molecular Simulations Inc. Pharmaceutical Development Consortium Meeting, March 1999.

"Analysis of Pharmaceutical Pick-Up Sticks Using Digital Thermal Video Microscopy", I. M. Vitez, A. W. Newman, M. Davidovich, R. L. Mueller at Eastern Analytical Symposium and Exposition, November 1998.

"Physical Characterization of a Solid Bulk Drug Substance Using a Multi-Disciplinary Approach", I. M. Vitez, W. P. Findlay, M. Galella, R. L. Mueller, A. W. Newman, B. Sarsfield, and A. K. Swensen at Eastern Analytical Symposium and Exposition, November 1998.

"Solving Characterization Problems in the Solid State using CERIUSt", A. W. Newman, I. M. Vitez, M. Davidovich, R. L. Mueller, K. L. Morris at Molecular Simulations Inc. Materials Characterization Seminar, September 1998.

"The Use of Scanning Electron Microscopy in the Characterization of Pharmaceutical Solids", R. L. Mueller, A. W. Newman, I. M. Vitez, C. Kiesnowski, D. E. Bugay, W. P. Findlay at Fine Particles Society, April 1998.

"Scanning Electron Microscopy as a Problem Solving Tool", R. L. Mueller, A. W. Newman, I. M. Vitez, C. Kiesnowski, D. E. Bugay, W. P. Findlay at Eastern Analytical Symposium and Exposition, November 1997.

"Physical Characterization of BMS-206XXX Precipitates", A. W. Newman, I. M. Vitez, M. Davidovich, R. L. Mueller, J. Z. Gougoutas, J. DiMarco, C. Rodriguez, D. E. Bugay, S. C. Fung, L. E. Schechler, S. A. Ranadive, K. S. Raghaven at BMS-PRI Scientific Poster Session, November 1997.

"BMS-206XXX Solid State Forms", R. G. Corrao, M. Davidovich, J. DiMarco, J. Z. Gougoutas, A. W. Newman, W. L. Parker, K. S. Raghaven, S. A. Ranadive, V. D. Sharma, I. M. Vitez at BMS-PRI Scientific Poster Session, November 1997

"The Use of Hot Stage Photomicroscopy in Crystal Form Characterization", I. M. Vitez, A. W. Newman, M. Davidovich, C. Kiesnowski at BMS-PRI Scientific Poster Session, November 1997.

"Crystal Structures of Solvates of BMS-212XXX", M. F. Malley, J. D. DiMarco, J. Grosso, H. N. Joshi, S. Modi, A. W. Newman, W. L. Parker, Z. Shi, J. Z. Gougoutas at BMS-PRI Scientific Poster Session, November 1997.

"The Evolution of Hot Stage Microscopy to Aid Solid State Characterization of Pharmaceutical Systems", I. M. Vitez, A. W. Newman, M. Davidovich, C. Kiesnowski at North American Thermal Analysis Society (NATAS), September 1997.

"Physical Characterization and Preliminary Quantitation of BMS-180048-02 Crystal Forms", A. W. Newman, I. M. Vitez, C. Kiesnowski, R. L. Mueller, J. DiMarco, J. Gougoutas at BMSIARC Conference, June 1997.

"Characterization of BMS-201XXX-04 Crystal Forms", A. W. Newman, R. Mueller, I. M. Vitez, C. Kiesnowski, D. E. Bugay, C. Rodriguez at BMS-PRI Scientific Poster Session, November 1996.

"Characterization of Pharmaceutical Solids Using an Integrated Hot Stage DSC Microscopy System", I. M. Vitez, A. W. Newman, C. Kiesnowski at BMS-PRI Scientific Poster Session, November 1996.

"Pre-Compaction and Lubrication Properties of PRUV (Sodium Stearyl Fumarate)", A. Ahmed, M. Celik, A. W. Newman, I. M. Vitez, C. Kiesnowski at AAPS Annual Meeting, October 1996.

"Applications of Hot Stage Microscopy in the Pharmaceutical Industry", I. M. Vitez, A. W. Newman at International Congress on Thermal Analysis and Calorimetry (ICTAC), August 1996.

"Characterization of BMS-193884 Crystal Forms", A. W. Newman, I. M. Vitez, C. Kiesnowski, D. E. Bugay, W. P. Findlay at BMSIARC Conference, June 1996.

"Starch and Starch Derivatives", A. W. Newman, R. L. Mueller, I. M. Vitez, C. Kiesnowski, D. E. Bugay, W. P. Findlay at BMS-PRI Scientific Poster Session, November 1995.

"The Effect of DSC Pan Configuration on the Thermal Characterization of Pharmaceuticals", I. M. Vitez, A. W. Newman at the AAPS Eastern Regional Meeting, June 1995.

"The Analytical Capabilities of the AR&D Materials Science Group in New Brunswick", I. M. Vitez, A. W. Newman, D. E. Bugay, J. DeVincentis, W. P. Findlay, C. Kiesnowski, R. L. Mueller, F. Rinaldi at BMSIARC Conference, June 1995.

"Physicochemical Properties of the Pure Magnesium Stearate Pseudopolymorphs", A. Ahmed, M. Celik, H. Brittain, A. Newman at the 1994 AAPS Annual Meeting, November 1994.

"Determination of Most Stable BMS-180291-02 Polymorphic Forms", A. W. Newman, I. M. Vitez, P. A. Cortina, D. E. Bugay, W. P. Findlay, G. Young at BMS-PRI Scientific Poster Session, November 1994.

"Evaluation of Pharmaceutical Polymorph Issues using Modulated Differential Scanning Calorimetry", I. M. Vitez, A. W. Newman, P. A. Cortina, G. Young at 23th Conference of the North American Thermal Analysis Society", September 1994.

"Pharmaceutical Solid and Particulate Characterization During Drug Development", A. W. Newman, P. Cortina, J. DeVincentis, I. Vitez, S. A. Ranadive, F. Rinaldi, D. E. Bugay at Fine Particle Society 25th Annual Meeting, July 1994.

"A Study of the Precompaction, Compaction, and Postcompaction Properties of Magnesium Stearate", A. Ahmed, G. Young, A. Newman, H. Brittain at BMS-PRI Scientific Poster Session, November 1993.

"Characterization of Water in BMS-181101-02 Drug Substance", S. J. Nicholson, A. B. Dennis, P. Timmons, P. York, K. R. Morris, A. W. Newman at BMS-PRI Scientific Session, November 1993.

"Characterization of Unknown Particulates in Bulk d-Sotalol HCl: A Collaborative Approach Utilizing FTIR Microscopy, Energy Dispersive X-Ray Analysis, and Polarizing Optical Microscopy", F. Rinaldi, D. Bugay, A. Newman, J. DeVincentis, H. Brittain at BMSIARC Conference, May 1993.

"Characterization of Taxol Crystalline Forms", A. W. Newman, K. R. Morris, D. E. Bugay, W. P. Findlay, G. V. Barbera, J. DeVincentis at BMS-PRI Scientific Session, November 1992.

"The Use of Anhydrous Lactose in Aqueous Granulation Processes", R. Wesdyk, A. W. Newman, N. C. Guma at AAPS 1992 Annual Meeting, November 1992.

"Effects of Lactose Type, Drug Solubility, Capsule Filling Machine Capsule Size, and Lubricant Concentration on Dissolution Stability", D. S. Desai, B. A. Rubitski, J. S. Bergum, A. W. Newman, S. A. Varia at AAPS 1992 Annual Meeting, November 1992.

"The Energetic and Structural Effect of Particle Size on the Characterization of Pharmaceutical Solids", K. R. Morris, A. W. Newman, D. E. Bugay, G. V. Barbera at Fine Particle Society 23rd Annual Meeting, July 1992.

"An Integrated Approach to the Salt Selection Process", K. Morris, A. Newman, M. Fakes, A. Thakur, A. Serajuddin, at Bristol-Myers Squibb Product Development Seminar, May 1992.

"The Use of Anhydrous Lactose in Aqueous-Based Granulation Processes", R. Wesdyk, A. Newman at Bristol-Myers Squibb Product Development Seminar, May 1992.

"Humidity-Dependent Changes in Crystalline Properties of an Organic Hydrate in Bulk Material and in Solid Dosage Forms", K. R. Morris, A. W. Newman, D. E. Bugay, S. A. Ranadive, M. Szyper, S. A. Varia, H. G. Brittain, A. T. M. Serajuddin at AAPS National Meeting, November 1991.

"Physical Interactions of Different Lubricants with Starch-Derived Disintegrants and Their Effects on Capsule Dissolution", D. S. Desai, B. A. Rubitski, S. A. Varia, A. W. Newman, K. R. Morris at AAPS National Meeting, November 1991.

"Quantitative Determination of Phase Composition of Cefepime", H. G. Brittain, D. E. Bugay, W. P. Findlay, A. W. Newman at BMSIARC Conference, June 1991.

"Solid State Characterization of Hygroscopic Compounds in Bulk and in Formulations", K. Morris, S. Ranadive, A. Newman, D. Bugay, M. Szyper at BMSIARC Conference, May 1991.

"Factors Effecting Differences in Film Thickness of Various Sized Beads Coated in Fluidized Bed Units", R. Wesdyck, Y. M. Yoshi, N. B. Jain, A. Newman at AAPS National Meeting, November 1990.

"Physical Characterization of Magnesium Stearate", H. G. Brittain, S. J. Bogdanowich, A. Winiecki Newman, J. DeVincentis at AAPS National Meeting, November 1990.

"Physical Characterization and Dehydration of Amiloride Hydrochloride Dihydrate", H. G. Brittain, A. Winiecki Newman at AAPS National Meeting, November 1990.

"Relationship Between the Physical and Mechanical Properties of Wet Granulated Microcrystalline Cellulose Following Drying", M. Chatrath, J. N. Staniforth, A. Winiecki Newman, H. G. Brittain at British Pharmaceutical Conference, September 1990.

"The Effect of Particle Size and Mass of Film Thickness of Beads Coated in Fluidized Bed Equipment", R. Wesdyck, Y. M. Yoshi, N. B. Jain, K. Morris, A. Winiecki at AAPS National Meeting, November 1989.

"Scanning Electron Microscopy, Thermogravimetry, and Luminescence Studies of Uranium Carbonate", D.L. Perry, H. G. Brittain, A. Winiecki at 197th ACS National Meeting, April 1989.

"Clay-Micelle Electrode for Catalytic Reduction of Organo-Halides", J. F. Rusling, C. N. Shi, A. M. Winiecki, S. L. Suib at ACS 195 National Meeting, June 1988.

"XPS Studies of Chemically Treated Aluminophosphate and Silicoaluminophosphate Molecular Sieves", A.M. Winiecki, S. L. Suib at ACS 192 National Meeting, August 1986.

"Surface States of Aluminophosphate and Zeolite Molecular Sieves", S. L. Suib, A. M. Winiecki, at Seventh International Zeolite Conference, August 1986.

"X-Ray Photoelectron Spectroscopy Investigations of Silica-Rich Zeolites", A. M. Winiecki, S. L. Suib at University of Connecticut Randolph T. Majors Memorial Lecture Series, October 1985.

"Hydroformylation of 1-Pentene with Rhodium Zeolites", S. L. Suib, S. Zhang, R. P. Zerger, A. M. Winiecki at ACS 188 National Meeting, August 1984.

"Photoassisted Catalytic Isomerization of 1-Pentene via Metal Carbonyl Zeolites", A. M. Winiecki, J. C. Baxter, S. L. Suib at University of Connecticut Randolph T. Majors Memorial Lecture Series, November 1983.

### **Webcasts**

"Amorphous Dispersions: What Are They and Will They Help?" A. Newman for Seventh Street Development Group, September 28, 2011.

"Form Selection: What Solid Form Should I Choose?" A. Newman for Seventh Street Development Group, August 1, 2011.

"Characterization: How Do I Know if I Have Polymorphs?" A. Newman for Seventh Street Development Group May 25, 2011.

"Polymorph Screening: How Do I Find New Forms?" A. Newman for Seventh Street Development Group, April 27, 2011.

"Hygroscopicity: Is My Form Hygroscopic?" A. Newman for Seventh Street Development Group, November 17, 2010.

"Solubility Improvement: Will Solid Forms Help My Solubility?" A. Newman for Seventh Street Development Group, November 23, 2010.

"Case Studies: What Happens When My Solid Form Changes?" A. Newman for Seventh Street Development Group, November 3, 2010.

"Formulation: Will My Solid Form Change?" A. Newman for Seventh Street Development Group Spring Webcast Series, June 2, 2010.

"Crystallization: How Do I Make the Right Form?" A. Newman for Seventh Street Development Group Spring Webcast Series, May 26, 2010.

"Salt Selection: How Do I Find New Salts?" A. Newman for Seventh Street Development Group Spring Webcast Series, May 19, 2010.

"Amorphous: What Do I Need to Know About Amorphous Materials" A. Newman for Seventh Street Development Group Spring Webcast Series, May 12, 2010.

"From a Beaker to a Bottle: Overview of the Drug Discovery and Development Process for Small Molecule Therapeutics" A. Newman for American Chemical Society Webinars Professional Growth Series, May 6, 2010.

"Solid Amorphous Dispersions: What Are They and Will They Help" A. Newman for Seventh Street Development Group Winter Webcast Series, February 9, 2010.

"Cocrystal Screening: How Do I Find Cocrystals" A. Newman for Seventh Street Development Group Winter Webcast Series, February 2, 2010.

"Drug Product Characterization: What Solid Form Is In My Formulation" A. Newman for Seventh Street Development Group Winter Webcast Series, January 28, 2010.

"Physical Stability: How Do I Know Which Form Is the Most Stable" A. Newman for Seventh Street Development Group Winter Webcast Series, January 19, 2010.

"Form Selection: What Solid Form Should I Choose" A. Newman for Seventh Street Development Group Winter Webcast Series, December 15, 2009 and January 14, 2010.

"Process Induced Transformations: Why Is My Form Changing" A. Newman for Seventh Street Development Group Fall Webcast Series, November 6, 2009.

"Cocrystal Properties: Will Cocrystals Help" A. Newman for Seventh Street Development Group Fall Webcast Series, October 22, 2009.

"Polymorph Screening: How Do I Find New Forms" A. Newman for Seventh Street Development Group Fall Webcast Series, October 16, 2009.

"Characterization: How Do I Know If I Have Polymorphs" A. Newman for Seventh Street Development Group Fall Webcast Series, October 8, 2009.

"What Are Polymorphs and Why Do We Care" A. Newman for Seventh Street Development Group Fall Webcast Series, September 22, 2009.

"Intellectual Property and Regulatory Considerations for Polymorphs" A. Newman for American Chemical Society Webcast Series on Polymorphism in Organic/Pharmaceutical Systems, August 18, 2009, November 10, 2009, November 11, 2010.

"Process Induced Transformations During Compound and Product Manufacture" A. Newman for American Chemical Society Webcast Series on Polymorphism in Organic/Pharmaceutical Systems, August 11, 2009, November 3, 2009, November 4, 2010.

"Developing a Formulation Process" A. Newman for American Chemical Society Webcast Series on Polymorphism in Organic/Pharmaceutical Systems, August 4, 2009, October 27, 2009, October 28, 2010.

"Developing a Crystallization Process" A. Newman for American Chemical Society Webcast Series on Polymorphism in Organic/Pharmaceutical Systems, July 28, 2009, October 20, 2009, October 21, 2010.

"Thermodynamic Stability of Polymorphs and Choosing the Best Form for Development" A. Newman for American Chemical Society Webcast Series on Polymorphism in Organic/Pharmaceutical Systems, July 21, 2009, October 13, 2009, October 14, 2010.

"Polymorph Screening" A. Newman for American Chemical Society Webcast Series on Polymorphism in Organic/Pharmaceutical Systems, July 14, 2009, October 6, 2009, October 7, 2010.

"Solid-State Characterization" A. Newman for American Chemical Society Webcast Series on Polymorphism in Organic/Pharmaceutical Systems, July 7, 2009, September 29, 2009, September 30, 2010, November 11, 2011.

"Introduction to Polymorphism" A. Newman for American Chemical Society Webcast Series on Polymorphism in Organic/Pharmaceutical Systems, June 23, 2009, September 22, 2009, September 23, 2010, November 10, 2011.

## Partial Crystallization Behavior during Spray Drying: Simulations and Experiments

D. Chiou, T. A. G. Langrish, and R. Braham

*School of Chemical and Biomolecular Engineering, The University of Sydney, Sydney, New South Wales, Australia*

Simulations of crystallization behavior in a spray dryer have been performed using modifications to a model developed by previous workers and applied to a Buchi-290 laboratory-scale dryer. The potential crystallization behavior has been modeled using Williams-Landel-Ferry kinetics. Explorations using the model have suggested that the air inlet temperature is an important variable affecting crystallization in the dryer. The explorations suggested drying conditions that permitted reasonable drying while controlling the degree of crystallization. These conditions were examined and tested experimentally, also showing that the apparent degree of crystallinity was affected by the inlet air temperature over the range of inlet temperatures from 134°C (~55% crystalline) to 210°C (~76% crystalline). The simulation also predicted the trends in the experimental results from previous workers where their experimental results are considered in terms of the measurement techniques used in each case, suggesting that the simulation is a reasonable tool for developing operating conditions for drying equipment to give low or high degrees of crystallinity in the products.

**Keywords** Crystallization; Drying; Particle; Simulation; Spray drying

### INTRODUCTION

New engineered powders in industries producing consumer, pharmaceutical, and food materials often face challenges due to powder stickiness, which may affect the flowability and the stability of the powders. It has been well known for many years<sup>[1]</sup> that spray-dried materials are mainly amorphous, and the stickiness of spray-dried powders causes significant problems with the deposition of powders on the walls of spray dryers.<sup>[2,3]</sup> Although crystalline powders may still stick to the walls of dryers due to van der Waals and electrostatic forces, a more crystalline product may reduce the amount of wall deposition compared with a more amorphous one. Reducing stickiness in materials can be achieved through partial or complete crystallization of the sticky components. It is thus

important to investigate the parameters affecting the crystallization process from amorphous products to control the degree of wall deposition. In addition, the degree of crystallinity in the solid matrix may be a fundamental factor that influences many other physical properties in spray-dried powders, such as porosity,<sup>[4]</sup> solubility,<sup>[5]</sup> and flowability.<sup>[6]</sup>

Studies of crystallization behavior in storage and at near-ambient conditions are numerous for lactose,<sup>[7–9]</sup> sucrose,<sup>[10]</sup> and for other materials,<sup>[11,12]</sup> but there are fewer references to crystallization being carried out in the drying process itself. The work by Hartel and coworkers<sup>[13,14]</sup> shows that crystallization can be carried out in the drying of thin sucrose films. Comparing freeze-dried and spray-dried amorphous lactose, Haque and Roos<sup>[7]</sup> observed different rates of crystallization at varying relative humidities, finding that spray-dried material underwent less sorption than the freeze-dried materials at high relative humidities and that spray-dried lactose crystallized faster than freeze-dried material. This suggests that more stable behavior may be given by spray-dried powders during storage and that spray-dried powders have different crystallization behaviors to freeze-dried ones, so the processing approach had a significant effect on the product properties.

Here the term *crystallization* is used to describe the behavior where spray-dried powder undergoes a transformation to a partially or completely crystalline solid. A partial crystalline solid is defined when the amorphous content is less than 100% as this is an indicator of crystallization behavior in progress. The above work carried out on crystallization in storage shows that it is due to material temperatures that are above the glass transition temperature, which is affected by the moisture content of the material and hence by the relative humidity and temperature of the surrounding environment. The work on the crystallization of solids in storage indicates that manipulation of the operating conditions in a dryer, and the properties of the feed, may allow the drying process itself to either minimize or maximize the degree of crystallinity in the

Correspondence: T. A. G. Langrish, School of Chemical and Biomolecular Engineering, The University of Sydney, Sydney, NSW 2006, Australia; E-mail: t.langrish@usyd.edu.au



products, rather than allow an amorphous material to crystallize in storage.

A common approach to studying crystallization kinetics is the use of the Avrami equation.<sup>[15]</sup> This equation is an exponential rate function for crystal growth and has been widely applied. The equation involves a parameter,  $k$ , which is not universal for different materials for nucleation, and a growth rate,  $n$  (2, 3, or 4), which is based upon the type of nucleation used to predict the crystallization behavior.<sup>[15]</sup> A study of the crystallization behavior for some amino acids<sup>[16]</sup> found that the thermal history of the material was not adequately accounted for when using primary and secondary nucleation models based on the Avrami equation, showing that the use of this equation has limitations.

An alternative approach to modeling solid-phase crystallization behavior, compared with the Avrami equation, is the Williams-Landel-Ferry equation (WLF).<sup>[17]</sup> This equation was based on the melting behavior of polymers and contains universal constants for a wide range of materials tested by Williams et al.<sup>[17]</sup> in polymers (polystyrene, polyisobutylene), organic (glucose, abietic acid, *n*-propanol, propylene glycol, glycerol), and inorganic (boron trioxide, sodium-lead silicate, sodium-calcium silicate) glasses. The same equation was then used effectively to model crystallization behavior for food powders like lactose.<sup>[9]</sup> Since the WLF equation has been successfully used before for lactose and contains constants that appear to be widely applicable to many materials, this is the approach for crystallization that will be considered in this work.

A drying simulation based on the use of the WLF equation may provide guidance for spray drying powders to either minimize or maximize their degrees of crystallinity, as desired for the final product use, within the drying process itself (as an in-process approach). Initially, even predicting the trends in the degree of crystallinity when the operating conditions are changed would be useful for guiding experimental studies without necessarily giving the absolute values for the extent of crystallinity, and this type of relative indication is provided by the following simulation.

Since there is a large amount of supporting literature on the properties and behavior of spray-dried lactose and its crystallization, it has been chosen as the main material to be spray dried in both the simulations and the experiments in this work. In addition, the limited experimental data from the literature on other materials have also been considered, which suggests that the partial or complete crystallization of amorphous components in these solids can be carried out to some extent in spray dryers.

## SPRAY DRYING SIMULATION

This simulation of spray drying behavior was based on work done by Hanus and Langrish,<sup>[18]</sup> but the parallel-flow nature of the simulation dates back to the work of Keey

and Pham.<sup>[19]</sup> The simulation incorporates mass, heat, and momentum balances for the drying of individual droplets and is based on the model by Truong et al.,<sup>[20]</sup> which is a steady-state simulation for the co-current spray drying of sugar-rich foodstuffs. The model here was modified by Hanus and Langrish<sup>[18]</sup> to more appropriately model the drying of sodium chloride, by incorporating a characteristic drying curve (drying kinetics) that is more appropriate for sodium chloride and also accounting for the heat loss from the spray dryer. Further modification has been included for lactose as the material being dried and for the crystallization rates using Williams-Landel-Ferry kinetics.

## Model Basis and Assumptions

The model assumes plug flow through the spray dryer from the inlet to the outlet. It is assumed that no backmixing of particles occurs. While this assumption is not strictly true, the plug-flow assumption was adequate to predict the wall deposition behavior in the work of Hanus and Langrish.<sup>[18]</sup> In addition, the simulation is intended to give an indication of the relative extents of crystallization at different operating conditions rather than the absolute amount of crystallinity. For exploring the effects of different operating conditions, the use of such a simple model for the drying behavior to predict the relative effect of different operating conditions has been found by workers in the past, such as Keey and Pham,<sup>[19]</sup> to be adequate, particularly for the tall-form design of spray dryer used here, where tall-form spray dryers have lengths that are of the order of five times their diameters.<sup>[21]</sup> This plug-flow reaction approach has known weaknesses in terms of the effects of different designs on the flow patterns in the dryers,<sup>[21]</sup> but these plug-flow approaches are computationally very tractable compared with computational fluid dynamics (CFD) simulations. Time-dependent CFD calculations, when properly performed, take days, weeks, and months,<sup>[22]</sup> while this plug-flow reactor approach can be solved in minutes.

The air temperature and humidity profiles along the cross section of the drying chamber are assumed to be uniform. The axial velocity is assumed to be uniform across each cross section area of the drying chamber, which is close to the turbulent flow profile except close to the wall, and the chamber Reynolds number (calculated as the average gas velocity through the dryer, multiplied by the dryer diameter of 0.155 m, and by the gas density, divided by the dynamic viscosity of the gas) is over 4000 in this equipment. In reality, the gas flow in the dryer is not completely steady, as is assumed in the model. One-way gas-droplet coupling is used, because the momentum of the water droplets contributes only a moderate percentage (7.3–20%, with an average of 13.7%) to the total momentum of air and water in the Buchi B-290 spray dryer.<sup>[23]</sup> As a result,

it is within reason to assume that the droplets do not significantly affect the gas flow patterns and the droplets follow the gas flow patterns according to droplet and particle trajectory calculations, as will be described in the following sections. It is also assumed that no agglomeration or breakup of droplets or particles takes place in the drying chamber, and these effects are likely to be small for the droplet concentrations (droplet and particle numbers per unit volume of gas) present in this dryer, according to collision rate estimates based on the work of Langrish and Kota.<sup>[24]</sup> These assumptions are the same as those reported in Truong et al.<sup>[20]</sup>

The numerical simulation incorporates a model for the droplet and particle drying kinetics. There are some suggestions that the amount of drying in most spray dryers is limited by equilibrium between the outlet gas and the dried particles (the “exhaust gas locus” concept),<sup>[25]</sup> and the observations of Jindal and Boonyai<sup>[26]</sup> and Ozmen and Langrish<sup>[27]</sup> for a pilot-scale dryer support this suggestion. However, there is also some evidence<sup>[28]</sup> that the drying performance of small-scale (pharmaceutical type) spray dryers, such as the Buchi B290 used here, is limited by the particle drying kinetics. The main approaches to predicting the drying kinetics for particles include the concept of a characteristic drying curve,<sup>[19,29]</sup> a shortcut solution to the diffusion equation,<sup>[30]</sup> and other diffusion models<sup>[2,31]</sup> or receding-plane type models.<sup>[32,33]</sup>

The numerical simulation used in this work uses the concept of a characteristic drying curve to predict the drying kinetics. On the basis of the reasonable performance of this model in the work of Keey and Pham<sup>[19]</sup> and Langrish and Kockel,<sup>[19]</sup> this approach is assumed to be adequate to represent the trends in the crystallization behavior, which depend on the moisture content and temperature of the droplets and particles between different operating conditions. The droplets contain solids, and it is therefore important to allow for hindered drying due to the presence of the solids. The general form of the characteristic drying curve<sup>[34]</sup> is that the relative drying rate ( $\xi$ ), which is the actual drying rate of the solids relative to the unhindered drying rate, is some function of the characteristic moisture content, as follows:

$$\begin{aligned} \xi &= f(\Phi) & \text{if } X \leq X_{cr} \\ \xi &= 1 & \text{if } X > X_{cr} \\ \Phi &= \frac{X - X_e}{X_{cr} - X_e} \end{aligned} \quad (1)$$

Here  $\Phi$  is the characteristic moisture content (–),  $X$  is the actual average moisture content of the particle ( $\text{kg kg}^{-1}$ ),  $X_{cr}$  is the critical moisture content ( $\text{kg kg}^{-1}$ ), and  $X_e$  is the equilibrium moisture content ( $\text{kg kg}^{-1}$ ). Below the critical moisture content of the droplet, hindered drying occurs. The equilibrium moisture content is the moisture

content of the particle in equilibrium with the gas, where no further reduction in moisture content occurs. More details of the model are given in Truong et al.<sup>[20]</sup> A quadratic falling rate curve ( $f = \Phi$ ) has been used in this work for lactose. The simulation equations are given in more detail in Hanus and Langrish<sup>[18]</sup> and include droplet and particle trajectories, mass and energy balances for the droplets, particles and the gas, and particle drying kinetics and heat transfer rate equations.

### Model Solution

The model, simulating co-current spray drying, and incorporating the experimentally estimated heat loss from the Buchi B-290 spray dryer, is a set of at least eight ordinary differential equations, with additional equations for each particle size class, representing the mass transfer rates and mass and energy balances for each size class. The equations were implemented and solved in Mathworks' Matlab package using the inbuilt Matlab stiff ordinary differential equation solver function, ode23s. The stiff equation solver, ode23s, uses the second- and third-order Runge-Kutta methods to solve the ordinary differential equations.

The initial and boundary value conditions of some parameters must be entered. The initial values of the radial and tangential components of the inlet air velocity were both set to  $0 \text{ ms}^{-1}$ , because the air forced into the dryer is introduced axially. The initial values of other parameters, such as axial components of the inlet air velocity and inlet air temperatures, were based on the experimental conditions used and described in the following sections.

### Crystallization Kinetics and the Williams, Landel, and Ferry Equation

As previously mentioned, actual measurements of, and correlations for, the rate of crystallization of polymers, organic glasses and inorganic were reported by Williams, Landel and Ferry (WLF)<sup>[17]</sup> and used to form the WLF equation. Roos and Karel<sup>[9]</sup> were able to apply the equation to food polymers, such as lactose. They found that the ratio ( $r$ ) of the time for crystallization ( $\theta_{cr}$ ; time taken for the material to become 100% crystalline) at any temperature ( $T$ ) to the time for crystallization ( $\theta_g$ ) at the glass transition temperature ( $T_g$ ) could be correlated by the following equation (the WLF equation):

$$\log_{10} r = \log_{10} \left( \frac{\theta_{cr}}{\theta_g} \right) = \frac{-17.44(T - T_g)}{51.6 + (T - T_g)} \quad (2)$$

Since the ratio,  $r$ , decreases when crystallization becomes more rapid, the inverse of this ratio is a measure of the relative rate of crystallization, compared with the crystallization rate at the glass transition temperature. The inverse of this ratio can be described as the “impact” of the particle temperature,  $T$ , and the glass transition temperature,  $T_g$ ,

which is a function of the particle moisture content,  $X$ , through the Gordon-Taylor equation. Both the particle temperature,  $T$ , and the particle moisture content,  $X$ , change through the dryer, as described in the previous sections, so the glass transition temperature,  $T_g$ , also changes as the droplets and particles dry out when they move through the dryer.

The Gordon-Taylor equation<sup>[35]</sup> can be used to predict the glass transition temperature of food mixtures and pharmaceutical solids as a function of the composition and the glass transition temperatures of the individual components that make up the mixture:

$$T_g = \frac{w_1 T_{g1} + k w_2 T_{g2}}{w_1 + k w_2} \quad (3)$$

where  $w_1$  and  $w_2$  are the respective weight fractions of the two components,  $T_{g1}$  is the glass transition temperature of one component,  $T_{g2}$  is the glass transition temperature of the other component, and  $k$  is a curvature constant, which can be determined empirically. One of these components may be the solid material that is spray dried, while the other might be the moisture in the particle, and the equation can be extended to three or more components in the particle.<sup>[36]</sup> This equation is based on the assumption of perfect volume additivity, that is, the liquids mix without any change in volume, and there is no specific interaction between the components of the mixture. The equation has been used by many workers to predict that the glass transition temperature decreases with increasing moisture content, as is found experimentally. The glass transition temperature is affected by the nature and composition of the components.<sup>[8,9]</sup> The weight fraction of water,  $w$ , is related to the moisture content,  $X$ , expressed on a dry basis, through the equation  $w = X/(1 + X)$ .

As mentioned previously, both the particle temperature and the particle moisture content change through the dryer, and these changes are predicted by the simulation. These changes mean that the local value of the impact, the inverse of the ratio of crystallization times, needs to be integrated over the residence time for each particle in the dryer. In effect, this procedure treats the WLF equation (2) as representing the inverse of a rate equation for crystallization, where the inverse of the ratio is equivalent to a relative rate for crystallization, and the inverse of the ratio is integrated over the residence time of each particle in the dryer to predict the overall increase in crystallinity. It is important to note that the WLF equation (Eq. (2)) makes no distinction between nucleation and crystal growth, meaning that it is implicitly assumed that nucleation of the material is non-rate-limiting.

### Simulation Parameters

The ranges of operating variables considered were as follows, being the general limits for the normal operation

of the Büchi-290 laboratory-scale spray dryer used here for experiments and described in the following section in more detail:

Inlet air temperature (°C), range 75–220°C  
 Aspirator rate (% flow), range 50–100% (19–37.5 m<sup>3</sup>/h)  
 Nozzle rotameter (mm), range 10–60 mm (35 mm ~ 500 L/h)  
 Peristaltic pump rate (% speed), range 1–50% (25% ~ 8.8 mL/min)  
 Feed concentration (% solids), range 1–50% (w/v%)

The solutions of the simulations produced the outlet moisture content of the particles and the indicator of crystallization, labeled as the impact ratio, integrated over the residence time in the dryer for each particle and averaged according to the numbers of particles in each size class, for the operating conditions used in each experiment.

### EXPERIMENTAL METHODS

Production of lactose samples using conditions suggested by the model was performed with a Büchi-290 laboratory-scale spray dryer (Büchi, Flawil, Switzerland). The samples were tested for the degree of crystallinity (the amount of material in partial or complete crystalline form) immediately after spray drying. Lactose was chosen as the test material due to the literature having a significant amount of data on the solid-phase crystallization behavior in storage for this material. The degree of crystallinity in the powders was determined using water-induced crystallization (WIC), modulated differential scanning calorimetry (MDSC), X-ray diffraction (XRD), and pore size distributions (PSD), and the details of the techniques, equipment, and their operating principles are summarized in Table 1.

### RESULTS AND DISCUSSION

#### Trends in the Simulation Results

Simulation solutions for changes in the inlet air temperature from 70 to 220°C have been generated, with the fixed variables being an aspirator (main air flow) rate of 100% (0.0149 kg·s<sup>-1</sup>), a nozzle air rotameter setting (nozzle air flow rate) of 52 mm (19.9 L·min<sup>-1</sup>), a pump rate (liquid flow rate) of 22% (0.000103 kg·s<sup>-1</sup>), and a solution concentration of 15% (w/v%). There are at least two competing effects in Fig. 1. As the inlet air temperatures increase, the particle temperatures increase, which is one effect. The moisture contents also decrease as the inlet air temperatures increase, increasing the glass transition temperature, which is the second effect. However, the moisture contents cannot physically decrease below zero, so the glass transition temperatures cannot increase above the dry value of the glass transition temperature for lactose of 101°C. Hence the difference between the particle and glass transition temperatures increases as the inlet air

TABLE 1  
Techniques used for the crystallinity measurements in this work

Method for crystallinity measurement	Equipment	Principle
Water-Induced Crystallisation (WIC)	Controlled humidity environment (saturated sodium chloride salt solution ~ 70% relative humidity, Winston & Bates, 1960); mass measurements taken continuously by computerised data-logging (four decimal figure analytical balance, Mettler-Toledo AB204S).	Greater sorption and desorption indicate greater amorphous content (Jouppila & Roos, 1994; Chiou & Langrish, 2007).
Modulated Differential Scanning Calorimetry (MDSC)	Hermetically sealed pans, heated from 40°C to 300°C using ramp rate of 10°C/min with 1°C modulated signal every 60 seconds (TA Instruments Q1000).	Heat absorbed by samples during phase transition.
X-Ray Diffraction (XRD)	Siemens Diffraktometer D5000; scanning range set to 10–70°, step size 0.02°, scanning rate of 1 step/second 40 kV and 30 mA.	Diffacted X-ray angles are characteristic of spacing between planes of atoms & molecules in material.
Pore Size Distributions (PSD)	QuantaChrome Autosorb-1 machine; nitrogen used as adsorbate at outgas temperature of 60°C for 22 hours with liquid nitrogen bath at – 196°C; thirty relative pressure points measured.	Gas volumes measured; calculations of surface area indicate pore size distribution; amorphous powders tend to have greater pore sizes available, greater sorption capacity compared with crystalline states of same material (Trivedi & Axe, 2001).

temperature increases. These increases in the differences between the particle and glass transition temperatures raise the predicted rates of crystallization, increasing the impact values as the inlet air temperatures increase. The model solutions therefore appear to be physically reasonable.

#### Experimental Testing of Simulation Predictions

Experimental testing of these predictions was conducted. Two sets of conditions were used, altering only the

inlet air temperature, while the other operating conditions were kept the same. The inlet air temperature for the amorphous condition was initially suggested to be 134°C, while the inlet temperature for the crystalline condition was set to 210°C because Fig. 1 shows that the model predicts high degrees of crystallinity at these relatively high temperatures, due mainly to the increase in particle temperature at higher inlet air temperatures. The conditions used for the two sets of experiments were inlet air temperatures of 134 and 210°C, an aspirator rate of 100% ( $0.0149 \text{ kg} \cdot \text{s}^{-1}$ ), a nozzle setting of 52 mm ( $19.9 \text{ L} \cdot \text{min}^{-1}$ ), a pump rate of 23% ( $0.000106 \text{ kg} \cdot \text{s}^{-1}$ ), and a solution concentration of 15% solids (w/v%).

The sample powders were then analyzed for their sorption behavior, as described previously. The peaks in Fig. 2 have been adjusted on the time axis so their maximum heights were horizontally aligned. There is a distinct overlap of the maximum change in the moisture contents for the crystalline condition (210°C) between 8.3 and 8.49%, for three repeated experiments at the same conditions. The moisture content peaks for the amorphous conditions (134°C) were measured to be 8.76–9.3%, also for three repeated experiments at the same conditions. The simulation solutions for these two conditions produced impact ratios of 8.3 (134°C) and 10.6 (210°C). The trends in these

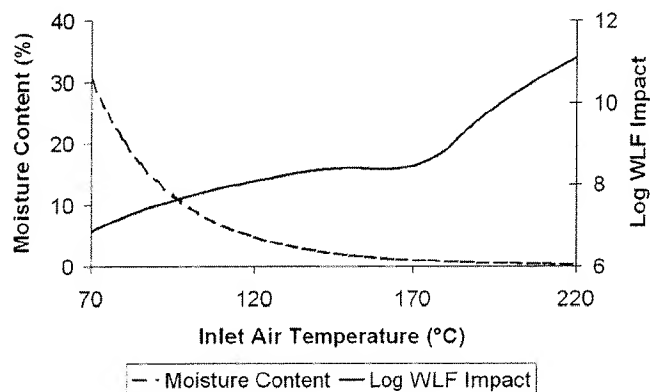


FIG. 1. WLF impact ratio values and moisture content from simulation solutions for inlet air temperature changes.

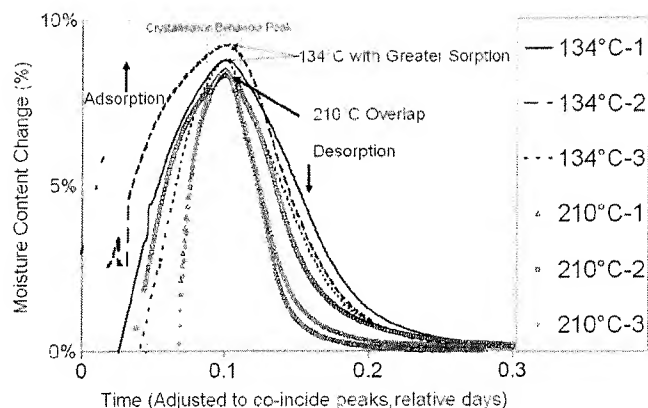


FIG. 2. Sorption data for amorphous and crystalline spray drying conditions.

impact ratios suggest that the model predictions of greater crystallinity at 210°C, compared with lower crystallinity at 134°C, have been experimentally supported.

The greater amounts of moisture were absorbed before the crystallization transformation occurred in the water-induced crystallization process suggest that the powders from the lower temperature conditions for spray drying are more amorphous than the powders from spray drying at the higher temperatures. This behavior is consistent with the known hygroscopic behavior previously seen in amorphous powders and materials.<sup>[6,37]</sup> The internal structure of amorphous powders is disordered, and moisture acts as a lubricant to allow crystallization of the powders to occur. As crystallization occurs, moisture is lost, since the crystalline powders can hold less moisture as part of their ordered crystalline structures, and desorption of moisture from the powders occurs, even at a constant relative humidity.<sup>[8,9,38]</sup>

Confirmation that these sorption tests were reflecting the differing degrees of crystallinity was carried out by XRD, MDSC, and pore size analysis. The XRD scans produced significant variation, since some mechanical damage to the sample was unavoidable during preparation, even though this damage was minimized as far as possible. Analysis of the lactose samples conducted with MDSC provided additional information on the crystalline state

of the powders. Table 2 shows the results of these additional studies carried out using XRD and MDSC.

Pore size distribution (PSD) studies on three samples for each of the two conditions generated the results shown in Fig. 3. The PSD of the powders can be related to the presence of amorphous and crystalline material. The more crystalline forms of the powders, having a more compact structure, tend to have smaller pores, reducing the amount of gas sorption possible.<sup>[4]</sup> The powders created at an inlet air temperature of 134°C (dotted lines) had a larger pore size than those at 210°C (solid lines) seen in the two dotted lines (runs 1 and 3) with higher pore volumes than the solid lines representing the 210°C conditions, although run 2 is an anomaly. Although run 2 does not overlap with runs 1 and 2 from the same conditions in Fig. 3, it remains an anomaly only in the PSD study since the results from Fig. 2 are consistent with the other two 134°C condition runs, being more amorphous with greater sorption behavior. The remaining two runs from the 134°C conditions overlap well, supporting the suggestion that the 134°C samples are more amorphous, since these measured pore sizes are greater than the more crystalline 210°C samples.

The four techniques used for the determination of crystallinity all suggest that the trends in the predictions from the simulation are reasonable. Samples with lower crystallinity from an inlet air temperature of 134°C were found to have greater moisture sorption, lower XRD peaks, greater PSD, and lower MDSC energies compared with the 210°C samples. These data are consistent with the simulation solutions by indicating that more crystalline powders are produced at a higher inlet air temperature.

#### Comparison with the Literature

The model was used to simulate the experiments performed by Harjunen et al.,<sup>[39]</sup> Chidavaenzi et al.,<sup>[40]</sup> Forbes et al.,<sup>[41]</sup> and Chan et al.<sup>[42]</sup> The material properties (heat capacities, liquid densities and viscosities, and glass transition temperatures) were adapted for use with ethanol as a solvent (for Harjunen et al.<sup>[39]</sup>) with physical constants found in the CRC handbook<sup>[43]</sup> and for use with as a solute mannitol (the Gordon-Taylor equation for predicting the

TABLE 2  
Results of crystallinity measurements using XRD and MDSC

Method for crystallinity measurement	Original crystalline form	Spray dried at 134°C	Spray dried at 210°C
X-Ray Diffraction (XRD), counts per second	210 (100%)	110 (52%)	130 (62%)
Modulated Differential Scanning Calorimetry (MDSC), J/g	508 (100%)	277 (55%)	385 (76%)

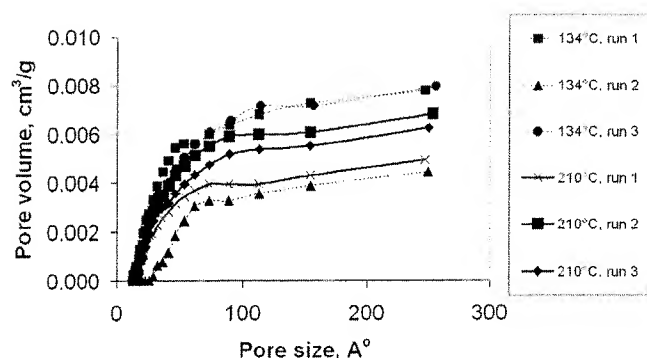


FIG. 3. Pore size distributions for lactose powders produced at 134 and 210°C.

value of  $k$  came from Roos,<sup>[44]</sup> the glass transition temperatures came from Chan et al.<sup>[42]</sup> as the primary material (for Forbes et al.<sup>[41]</sup> and Chan et al.<sup>[42]</sup>). Although in both Forbes et al.<sup>[41]</sup> and Chan et al.<sup>[42]</sup> the materials being spray dried were not pure mannitol/lactose, the simulation results can still account for the crystallization behavior of those materials under those conditions, on the assumption that the effects of the non-mannitol/lactose material would have a consistent effect on drying and crystallization for the final products at different operating conditions for the same equipment. The impact ratio and moisture content values are seen in Table 3.

The resulting trends in the impact ratios from the simulation corresponded with the experimental data for Forbes et al.,<sup>[41]</sup> with the higher concentration of mannitol being predicted to show more crystallization compared with the lower concentration of lactose. The results of the simulations for the work of Chan et al.<sup>[42]</sup> were similar, in that with a decreasing glass transition temperature for the feed solution, the impact ratio increased. Although the concentration of mannitol under the same conditions increased, the impact ratio did not completely reflect this situation, since the calcitonin component had a higher glass transition temperature and decreased the impact ratio value and likelihood of crystallization in the simulation. The simulation did give the expected result for pure mannitol, with a higher impact value than any of the other feed mixtures since the glass transition temperature for mannitol was significantly lower than the other mixtures. Based on the glass transition temperatures given in Chan et al.,<sup>[42]</sup> the simulation gave predictions that showed a gradual increase in the impact ratio values with decreasing glass transition temperatures. The predicted outlet moisture contents were the same, since the feed solids concentration was a constant value and only the glass transition temperature values were modified for the experiments.

The experimental data from Chidavaenzi et al.<sup>[40]</sup> showed that, with an increasing concentration of lactose,

more crystallization was found, similar to the results for mannitol by Chan et al.<sup>[42]</sup> However, the impact ratio given by the simulation did not directly predict this outcome. The initial impact ratio for the lowest concentration (10%) was the highest, with low predicted outlet moisture contents. However, with increasing concentration (20–40%), the lower impact ratios remained the same, with large increasing moisture contents (10% concentration had a moisture content of 1.3%, 20–40% concentration had a moisture content of 3.5–9.5%). It is possible that, with such high moisture content in the powders, some form of water-induced crystallization may have occurred after drying and before the measurements of the degree of crystallinity, especially since their experimental method involved equilibrating the samples prior to testing in a 75% relative humidity condition, which has been shown to cause water-induced crystallization in lactose.<sup>[8,12]</sup>

The work by Harjunen et al.<sup>[39]</sup> using water and ethanol mixtures to crystallize amorphous lactose was also tested by the simulation, with an unexpected result. The model predicted impact ratios indicating that the conditions used with a pure ethanol solvent would produce a powder of similar crystallinity to that from the (different) conditions with water as solvent. This result was in contrast to the experimental data by Harjunen et al.<sup>[39]</sup> However, lactose is very insoluble in pure ethanol (0.5–2 mg/mL),<sup>[45,46]</sup> so the spray-drying experiment by Harjunen et al.,<sup>[39]</sup> using a suspension of 15% w/v of lactose solids in pure ethanol, may mean that the lactose was being spray dried as a slurry instead of as a solution. If the lactose material was already crystalline in the slurry prior to spray drying, then it is possible that it may have remained crystalline after drying as well. Plots of the simulation outputs for water and ethanol solvent are shown in Figs. 4 and 5 (particle temperature) and 6 and 7 (particle temperature–glass transition temperature).

The plots explain why the ethanol solvent experiment did not produce a higher impact factor from the simulation, as expected. Comparisons of the particle temperatures and moisture contents in Figs. 4 and 5 show that, for spray drying with ethanol as a solvent, the particle temperatures are lower by nearly 30°C in the case of the largest particle size category. Figures 6 and 7 show the predicted temperature differences between the particle and the glass transition temperatures. The particles from the ethanol mixture are predicted to be at a temperature lower than the glass transition temperature of lactose, while the particles from the water mixture are predicted to be at a temperature that is 20°C above the glass transition temperature of lactose. At 20°C above the glass transition temperature, rubbery behavior and melting is shown<sup>[3]</sup> and crystallization from particle temperature cooling can occur,<sup>[47]</sup> which suggests that the particles sprayed with water are more likely to crystallize than those from the ethanol solvent, due to the

TABLE 3  
Predicted impact ratio and final moisture contents for the experimental data from previous workers

Authors	Inlet air temp (°C)	Aspirator Rate (kg·s <sup>-1</sup> )	Pump rate (mL/min)	Nozzle flow rate (L/h)	Inlet conc. of material in solution (%)	Material	Experimental results	Impact ratio (log <sub>10</sub> impact ratio)	Predicted final moisture content (%)
Harjunen <i>et al.</i> (2002)	160	0.0134 (90%)	5 (18%)	700 (40 mm)	15 in water	Lactose	100% amorphous	7.9	0.5
Büchi 190 spray dryer	106–108 (106 used)	0.0134 (90%)	5 (18%)	700 (40 mm)	15 in ethanol	Lactose	100% crystalline	8.1	0.5
Modified Harjunen <i>et al.</i> (2002)	160	0.0134 (90%)	5 (18%)	700 (40 mm)	15 in ethanol	Lactose	Predicted to be crystalline	8.4	0.2
same conditions for spraying water but using ethanol as the solvent									
Chidavaenzi <i>et al.</i> (1997)	185–190 (185 used)	0.0122 (82%)	25%	400 (28 mm)	10	Lactose	100% amorphous	9.3	1.3
Büchi 190 spray dryer			28% 31% 36% (Varied to keep outlet temp. constant at 135°C as seen experimentally)		20 30 40		91% amorphous 89% amorphous 82% amorphous	8.7 8.7 8.7	3.5 6.8 9.5

Forbes <i>et al.</i> (1998)	200	0.0122 (82%)	16.7 (60%)	800 (43 mm)	4	Mannitol (insulin)	Crystalline	12.0	22.7 <sup>a</sup>
Chan <i>et al.</i> (2004)	125	0.0149 (100%)	5 (18%)	~ 533 (based on 60psi flow rate in data) (34 mm)	2	Lactose (insulin)	Amorphous	10.7	43.1 <sup>a</sup>
					1	Mannitol :	Amorphous	10.5	0.3 <sup>b</sup>
						Calcitonin in Ratio, T <sub>g</sub> 0 : 100, 147°C			
						10 : 90, 128°C	Amorphous	10.6	0.3
						30 : 80, 94°C	Amorphous	10.7	0.3
						50 : 50, 66°C	Amorphous	10.8	0.3
						70 : 30, 79°C	Some crystallinity	10.7	0.3
						90 : 10, 96°C	Crystalline	10.7	0.3
						100 : 0, 11°C	Crystalline	11.5	0.3

<sup>a</sup> This predicted moisture content is possibly unrealistic since the presence of insulin in the feed would assist in drying and reduction of the moisture content. No glass-transition data were available for the feed mixture to accurately predict the role of insulin during the drying. Any inaccuracies that such limitations in the model predictions introduce in terms of the predicted final moisture contents may not be too significant in terms of predicting the relative trends in the degrees of crystallinity between different operating conditions, which is the main purpose of the model.

<sup>b</sup> The moisture contents for these experiments are the same since the simulation output for moisture is based on the feed concentration solids. Since the glass-transition temperatures were the main variable changed for these experiments, the predicted final moisture contents were predicted to remain constant with the constant feed concentration.



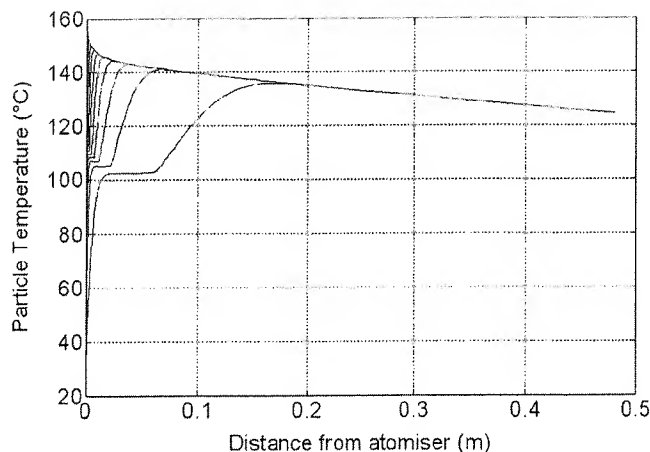


FIG. 4. Particle temperatures,  $T_{\text{part}}$ , predicted by the model as a function of distance through the dryer, water solvent.

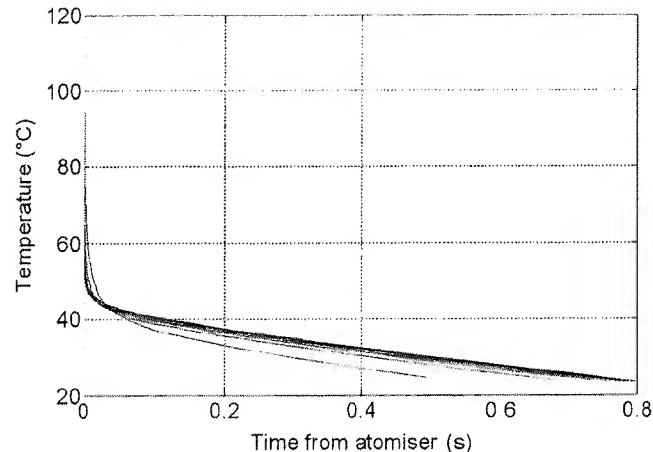


FIG. 6. Particle temperature - glass transition temperature,  $T_p - T_{\text{glass}}$ , predicted by the model as a function of distance through the dryer, water solvent.

differences in the inlet conditions between spray drying with water and with ethanol in the experimental data of Harjunen et al.<sup>[39]</sup>

For the same inlet and operating conditions for the spray dryer, the model was used to predict the differences in the impact ratio for the use of water as a solvent compared with ethanol. The simulations for the use of ethanol as a solvent confirmed that the higher inlet temperature, the same as that used for the drying with water, produced a greater impact ratio compared with the lower temperature for the drying with ethanol in the original experiments. The temperature differences between the particle and the glass transition temperatures (Fig. 8) are also consistent with this outcome, and the final particle temperatures with ethanol are predicted to be higher than those with water as the solvent. The predicted moisture contents of the

particles with ethanol are lower than those predicted with water, and this is expected since ethanol has a higher vapor pressure at the higher drying temperature in this simulation than in the experiments.

The model provides insights into the complex interactions involved in spray drying and crystallization. Larger changes in crystallization behavior can be caused by modifying the operating temperatures, with greater crystallization being given at higher temperatures, together with lowering the concentration of the feed material to give higher humidities in the drying air to give partial crystallization on particle surfaces. When the feed concentration was varied, with fixed inlet temperatures, the simulation predicted these changes in the impact ratio values for

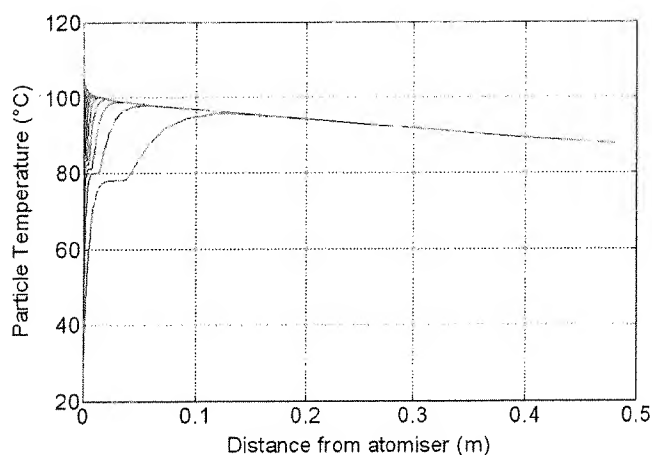


FIG. 5. Particle temperatures,  $T_{\text{part}}$ , predicted by the model as a function of distance through the dryer, ethanol solvent.

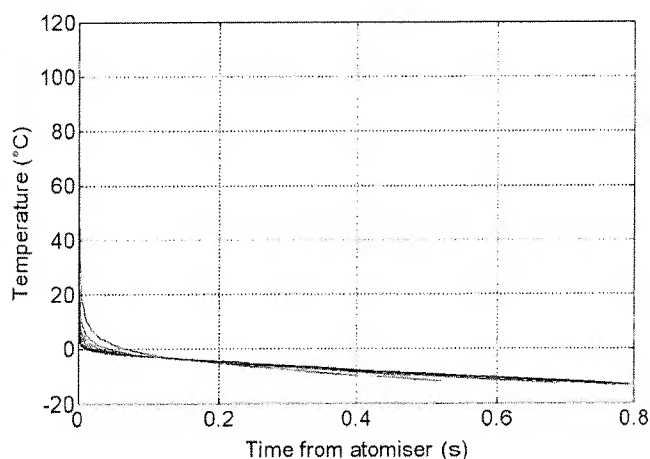


FIG. 7. Particle temperature - glass transition temperature,  $T_p - T_{\text{glass}}$ , predicted by the model as a function of distance through the dryer, ethanol solvent.

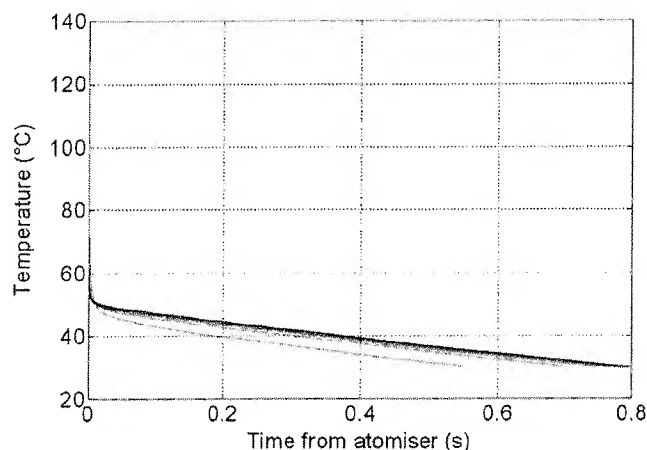


FIG. 8. Particle temperature – glass transition temperature,  $T_p - T_{\text{glass}}$ , for the ethanol solvent model as a function of distance through the dryer with water solvent conditions.

crystallization. The outlet moisture content will also increase when the air humidities increase, so this consideration may limit the extent to which the humidity can be increased. Smaller changes in crystallization behavior can also be achieved through the adjustment of pump rates and aspirator gas flow rates, since they do not appear to give such a large change compared with temperature and feed concentration changes. For example, a sensitivity analysis has shown that 1% changes in the inlet air temperature, feed concentration, and atomization gas flow rate caused the predicted impact ratios to change by approximately 0.2–0.38%, while the same percentage changes (1%) in the pump rate and aspirator values were predicted to give much smaller changes of approximately 0.025–0.033% in the impacts.

As previously discussed in the literature, it has been noted that changes in feed solvents (water, ethanol)<sup>[39]</sup> and feed mixtures with various compositions (PEG 4000,<sup>[11]</sup> proteins<sup>[41,42]</sup>) have shown significant changes of crystallization behavior within the spray dryer during the drying process. Extending the use of the simulation for other materials requires the input of the glass transition temperatures for the solvents and solutes, together with the interaction parameters ( $k$ ) between different components (solutes and solvents) for use in the Gordon-Taylor equation. The Williams-Landel-Ferry equation has parameters that appear to be universal for a wide range of materials.

## CONCLUSIONS

A simulation tool, using mass and energy balances and kinetics for heat and mass transfer and crystallization behavior, has suggested that the degree of crystallinity can be controlled in spray-dried products by adjusting

the operating conditions. The use of WLF kinetics for crystallization, at least in a relative and indicative sense and using the simulation to predict trends in the crystallization behavior, is supported by the experimental results, both here and from the literature, particularly where the experimental results are considered in terms of the techniques for the measurements used in each case. The simulation tool therefore appears to be useful for predicting trends in the partial or complete crystallization behavior of spray-dried products as the feed composition or the operating conditions in the spray dryer are changed.

## REFERENCES

1. White, G.W.; Cakebread, S.H. The glassy state in certain sugar-containing food products. *Journal of Food Technology* **1966**, *1*, 73–82.
2. Adhikari, B.; Howes, T.; Bhandari, B.R.; Troung, V. Surface stickiness of drops of carbohydrate and organic acid solutions during convective drying: Experiments and modeling. *Drying Technology* **2003**, *21* (5), 839–873.
3. Bhandari, B.R.; Datta, N.; Howes, T. Problems associated with spray drying of sugar-rich foods. *Drying Technology* **1997**, *15* (2), 671–684.
4. Trivedi, P.; Axe, L. Ni and Zn sorption to amorphous versus crystalline iron oxides: Macroscopic studies. *Journal of Colloid and Interface Science* **2001**, *244* (2), 221–229.
5. Pokharkar, V.B.; Mandpe, L.P.; Padamwar, M.N.; Ambike, A.A.; Mahadik, K.R.; Paradkar, A. Development, characterization and stabilization of amorphous form of a low  $T_g$  drug. *Powder Technology* **2006**, *167* (1), 20–25.
6. Chan, H.-K.; Chew, N.Y.K. Novel alternative methods for the delivery of drugs for the treatment of asthma. *Advanced Drug Delivery Reviews* **2003**, *55* (7), 793–805.
7. Haque, M.K.; Roos, Y.H. Crystallization and X-ray diffraction of spray-dried and freeze-dried amorphous lactose. *Carbohydrate Research* **2005**, *340*, 293–301.
8. Jouppila, K.; Roos, Y.H. Water sorption and time-dependent phenomena of milk powders. *Journal of Dairy Science* **1994**, *77* (7), 1798–1808.
9. Roos, Y.H.; Karel, M. Differential scanning calorimetry study of phase transitions affecting the quality of dehydrated materials. *Biotechnology Progress* **1990**, *6* (2), 159–163.
10. Kedward, C.; MacNaughtan, W.; Mitchell, J.R. Isothermal and non-isothermal crystallization in amorphous sucrose and lactose at low moisture contents. *Carbohydrate Research* **2000**, *329*, 423–430.
11. Chidavaenzi, O.C.; Buckton, G.; Koosha, F. The effect of co-spray drying with polyethylene glycol 4000 on the crystallinity and physical form of lactose. *International Journal of Pharmaceutics* **2001**, *216* (1–2), 43–49.
12. Chiou, D.; Langrish, T.A.G. Crystallisation of amorphous components of spray-dried powders. *Drying Technology* **2007**, *25*(9), 1423–1431.
13. Ben-Joseph, E.; Hartel, R.W. Computer modeling of sugar crystallization during drying of thin sugar films. *Journal of Crystal Growth* **1999**, *198–199* (2), 1294–1298.
14. Shastry, A.V.; Hartel, R.W. Crystallization during drying of thin sucrose films. *Journal of Food Engineering* **1996**, *30* (1–2), 75–94.
15. Piorkowska, E.; Galeski, A.; Haudin, J. Critical assesment of overall crystallisation kinetics theories and predictions. *Prog. Polym. Sci.* **2006**, *31*, 549–575.
16. Black, S.N.; Davey, R.J. Crystallisation of amino acids. *Journal of Crystal Growth* **1988**, *90*, 136–144.
17. Williams, M.L.; Landel, R.F.; Ferry, J.D. The temperature dependence of relaxation mechanisms in amorphous polymers and other

- glass-forming liquids. *Journal of the American Chemical Society* **1955**, *77* (14), 3701–3707.
18. Hanus, M.; Langrish, T.A.G. Re-entrainment of wall deposits from a laboratory-scale spray dryer. *Asia-Pacific Journal of Chemical Engineering* **2007**, *2* (2), 90–107.
  19. Keey, R.B.; Pham, Q.T. Behaviour of spray dryers with nozzle atomizers. *Chemical Engineer (London)* **1976**, *311*, 516–521.
  20. Truong, V.; Bhandari, B.R.; Howes, T. Optimization of co-current spray drying process of sugar-rich foods. Part I—Moisture and glass transition temperature profile during drying. *Journal of Food Engineering* **2005**, *71* (1), 55–65.
  21. Reay, D. *Fluid flow, residence time simulation and energy efficiency in industrial dryers*. Proceedings of 6th International Drying Symposium (IDS'88), Versailles, France, 1988.
  22. Fletcher, D.F.; Guo, B.; Harvie, D.J.E.; Langrish, T.A.G.; Nijdam, J.J.; Williams, J. What is important in the simulation of spray dryer performance and how do current CFD models perform? *Applied Mathematical Modelling* **2006**, *30*, 1281–1292.
  23. Best, S. *Understanding air flow patterns inside a pharmaceutical sized spray dryer*; Bachelor's thesis, School of Chemical and Biomolecular Engineering, University of Sydney, 2005; 31–32.
  24. Langrish, T.A.G.; Kota, K. A comparison of collision kernels for sprays from one and two nozzle atomisation systems. *The Chemical Engineering Journal* **2007**, *126* (2), 131–138.
  25. Bahu, R.E. Spray drying—Maturity or opportunities? Proceedings of International Drying Symposium (IDS'92), Montreal, Quebec, Canada, 1992; 74–91.
  26. Jindal, V.K.; Boonyai, P. *Effect of processing conditions on the quality of spray-dried soymilk*. Proceedings of Second Asia-Oceania Drying Conference, Pulau Pinang, Malaysia, 2001; 477–486.
  27. Ozmen, L.; Langrish, T.A.G. An experimental investigation of the wall deposition of milk powder in a pilot-scale spray dryer. *Drying Technology* **2003**, *21* (7), 1253–1272.
  28. Langrish, T.A.G.; Marquez, N.; Kota, K. An investigation and quantitative assessment of particle shape in milk powders from a laboratory-scale dryer. *Drying Technology* **2006**, *24* (12), 1619–1630.
  29. Langrish, T.A.G.; Kockel, T.K. Implementation of a characteristic drying curve for milk powder using a computational fluid dynamics simulation. *Chemical Engineering Journal* **2001**, *84* (1), 69–74.
  30. Liou, J.K.; Bruin, S. An approximate method for the nonlinear diffusion problem with a power relation between the diffusion coefficient and concentration I. Computation of desorption times. 2. Computation of the concentration profile. *International Journal of Heat and Mass Transfer* **1982**, *25* (8), 1209–1229.
  31. Chen, X.D. Heat-mass transfer and structure formation during drying of single food droplets. *Drying Technology* **2004**, *22* (1–2), 179–190.
  32. Chen, X.D.; Farid, M.; Reid, D.; Fletcher, A.; Pearce, D.; Chen, N.X. *A new model for the drying of milk droplets for fast computation purposes*. Proceedings of Chemeca '99, Rotorua, New Zealand, 1999; 825–830.
  33. Keey, R.B.; Suzuki, M. On the characteristic drying curve. *International Journal of Heat and Mass Transfer* **1974**, *17* (163), 1455–1464.
  34. Keey, R.B. *Introduction to Industrial Drying Operations*; Pergamon Press: Oxford, UK, 1978.
  35. Gordon, M.; Taylor, J.S. Ideal copolymer and the second-order transition of synthetic rubbers. I Non-crystalline copolymers. *Journal of Applied Chemistry* **1952**, *2*, 493–500.
  36. Arvanitoyannis, I.; Blanshard, J.M.V.; Ablett, S.; Izzard, M.J.; Lillford, P.J. Calorimetric study of the glass transition occurring in aqueous glucose:fructose solutions. *Journal of the Science of Food and Agriculture* **1993**, *63* (2), 177–188.
  37. Bronlund, J.; Paterson, T. Moisture sorption isotherms for crystalline, amorphous and predominantly crystalline lactose powders. *International Dairy Journal* **2004**, *14*, 247–254.
  38. Slade, L.; Levine, H. Beyond water activity: Recent advances based on an alternative approach to the assessment of food quality and safety. *Critical Reviews in Food Science and Nutrition* **1991**, *30* (2,3), 115–360.
  39. Harjunen, P.; Lehto, V.; Valisaari, J.; Lankinen, T.; Paronen, P.; Jarvinen, K. Effects of ethanol to water ratio in feed solution on the crystallinity of spray-dried lactose. *Drug Development and Industrial Pharmacy* **2002**, *28* (8), 949–955.
  40. Chidavaenzi, O.C.; Buckton, G.; Koosha, F.; Pathak, R. The use of thermal techniques to assess the impact of feed concentrations on the amorphous content and polymorphic forms present in spray dried lactose. *International Journal of Pharmaceutics* **1997**, *159*, 67–74.
  41. Forbes, R.T.; Davis, K.G.; Hindle, M.; Clarke, J.G.; Maas, J. Water vapor sorption studies on the physical stability of a series of spray-dried protein/sugar powders for inhalation. *Journal of Pharmaceutical Sciences* **1998**, *87* (11), 1316–1321.
  42. Chan, H.-K.; Clark, A.R.; Feely, J.C.; Kuo, M.-C.; Lehrman, R.; Pikal-Cleland, K.; Miller, D.O.; Vehring, R.; Lechuga-Ballesteros, D. Physical stability of salmon calcitonin spray-dried powders for inhalation. *Journal of Pharmaceutical Sciences* **2004**, *93* (3), 792–804.
  43. CRC. (1977). *CRC Handbook of Chemistry and Physics*, 58th Ed.; CRC Press: Palm Beach, FL.
  44. Roos, Y.H. Melting and glass transitions of low molecular weight carbohydrates. *Carbohydrate Research* **1993**, *238*, 39–48.
  45. Berner, B.; Otte, J.H.; Mazzenga, G.C.; Steffens, R.J.; Ebert, C.D. Ethanol:water mutually enhanced transdermal therapeutic system I: Nitroglycerin solution properties and membrane transport. *Journal of Pharmaceutical Sciences* **1989**, *78* (4), 314–318.
  46. Majd, F.; Nickerson, T.A. Effect of alcohols on lactose solubility. *Journal of Dairy Science* **1976**, *59* (6), 1025–1032.
  47. Wunderlich, B. *Crystal Nucleation, Growth, Annealing*; Academic Press: New York, 1976.
  48. Buckton, G.; Chidavaenzi, O.C.; Koosha, F. The effect of spray-drying feed temperature and subsequent crystallization conditions on the physical form of lactose. *AAPS PharmSciTech Report* **2002**, *3* (4), 1–6.

## The use of thermal techniques to assess the impact of feed concentration on the amorphous content and polymorphic forms present in spray dried lactose

Owen C. Chidavaenzi <sup>a</sup>, Graham Buckton <sup>a,\*</sup>, Fariba Koosha <sup>b</sup>, Ram Pathak <sup>b</sup>

<sup>a</sup> Centre for Materials Science, School of Pharmacy, University of London, 29–39 Brunswick Square, London, WC1N 1AX, UK

<sup>b</sup> SmithKline Beecham Pharmaceuticals, Yew Tree Bottom Road, Great Burgh, Epsom, Surrey, UK

Received 15 January 1997; received in revised form 14 August 1997; accepted 15 August 1997

---

### Abstract

The influence of feed concentration (covering solutions and suspensions) on the physical forms of lactose obtained by spray drying was investigated. Isothermal microcalorimetry was used to assess the heats of crystallisation of the amorphous materials, which enabled the determination of the % amorphous content. Differential scanning calorimetry (DSC) provided qualitative data for the lactose polymorphs that were present in the spray dried products. Lactose monohydrate content was determined thermogravimetrically. The lactose which was dissolved was solidified as the amorphous form, due to the rapid drying conditions. The amorphous contents for the suspension feed concentrations were higher than the amount of lactose dissolved, which was due to a milling effect on the suspended lactose particles in the atomiser. The milling resulted in formation of amorphous material by solid state transition, or enhanced solubility or more likely a combination of both. Only the sample with the highest feed concentration contained small amounts of lactose monohydrate due to incomplete dehydration of the lactose in suspension. The presence of anhydrous lactose was due to the high inlet air temperatures causing dehydration of the lactose monohydrate which was in suspension. Variation of feed concentration during spray drying leads to products with different % amorphous contents and different proportions of crystalline forms. Beta lactose was not detected, either because it was absent or present in quantities below the detection limits of the thermal methods. The spray drying process is now better understood as a process that leads to loss of crystallinity in materials, possibly by a combination of rapid solidification of dissolved material and solid state transitions due to milling effects in the atomiser. © 1997 Elsevier Science B.V.

**Keywords:** Amorphous; Polymorphism; Lactose; Spray drying; Crystallisation; Microcalorimetry; Differential scanning calorimetry; Thermogravimetric analysis

---

\* Corresponding author.

## 1. Introduction

### 1.1. Spray drying

Spray drying is a technique of importance in pharmaceutical industry, however the nature of the process is such that physical and chemical changes can occur in materials. The process involves the transformation of feed material from a fluid state into a dried particulate form by spraying the material into a drying air stream. Materials undergoing spray drying are processed via the following stages; atomisation of feed material, spray–air contact, drying of the spray material and separation of the material from the air stream. The process operational variables include; inlet air moisture, inlet temperature, feed rate, outlet temperature, air flow rate, feed concentration and atomisation pressure. A detailed description of spray drying is available elsewhere (Masters, 1990). Increasing the atomiser pressure creates smaller droplets at constant feed rate, resulting in high density fine particles. An increase in feed rate at constant operating conditions produces generally coarse spray particles and a wet product, due to inefficient drying. The nature of the spray dried product also depends on the properties of the feed material, where an increase in feed solids increases feed viscosity, which in turn produces coarse sprays on atomisation. An increase in feed solids usually results in an increase in particle size and bulk density. However, an increase in feed temperature may reduce feed viscosity causing a decrease in droplet size produced in the atomiser. This may improve atomisation efficiency of the process due to a slight reduction of the initial feed warm up period (Masters, 1990). The impact of feed concentration on the amorphous content and the different forms of the spray dried product, has seldom been studied in great detail. It is for this reason that this investigation was undertaken.

### 1.2. Characteristics of amorphous lactose

Pharmaceutical manufacturing techniques such as spray drying can produce materials in the amorphous state. Because the amorphous state is metastable with respect to the crystalline form,

phase transformations are likely to occur within the shelf life of the pharmaceutical product. These transformations usually result in loss of quality and potency in the product (Van Scoik and Carstensen, 1990).

Amorphous lactose produced by spray drying was found to have compaction properties which differed significantly from that of its crystalline forms (Vromans et al., 1986). Amorphous lactose is physically unstable above its glass transition temperature ( $T_g$ ) which is above most operating conditions. Numerous publications have demonstrated the physical instability of amorphous lactose at various relative humidities (e.g., Briggner et al., 1994; Buckton and Darcy, 1995, 1996; Sebhatu et al., 1993) due to the absorbed water plasticising the lactose such that  $T_g$  falls to or below room temperature. The critical relative humidity at which  $T_g$  falls below 25°C is quoted in most publications as around 48% RH. The effects of small quantities of moisture are not easily quantified; therefore, there is an uncertainty about the long term stability of amorphous lactose in pharmaceutical dosage forms. It was thought previously that glassy materials were stable below their glass transition temperature. However, molecular mobility at up to 50°C below the  $T_g$  of indomethacin, sucrose and polyvinyl pyrrolidone has been reported by Hancock et al., 1995. Such mobility may take place in amorphous lactose, which may have serious implications for the stability of products.

Although many studies have been undertaken on spray dried lactose, the impact of the feed concentration on the percentage amorphous content and the different lactose forms has been largely overlooked. It is thus the aim of this investigation to probe the effect of variation in feed concentration on the physical properties of the product.

## 2. Materials and methods

### 2.1. Materials

$\alpha$ -Lactose monohydrate (ex Smithkline Beecham, Great Burgh, Epsom, UK, batch E00131)

was used to prepare the spray dried samples and as a reference material for TGA, microcalorimetry and DSC experiments,  $\beta$ -lactose (Sigma, USA) was used in DSC experiments as a reference material.

## 2.2. Spray drying

Feed samples were prepared to give concentrations of 10 g/100 ml, 20 g/100 ml, 30 g/100 ml and 40 g/100 ml in distilled water. A Buchi 190 spray drier was used to prepare the samples from the different feed concentrations. The spray drying variables (Table 1), were kept constant, except for the feed rate which was varied for each feed concentration so as to minimise fluctuations in the outlet temperature.

The materials were collected and immediately desiccated over silica gel. The particle sizes of feed material and spray dried products were measured using laser diffraction (Malvern 2600C).

## 2.3. Isothermal microcalorimetry measurements

The microcalorimeter used was the 2277 Thermal Activity Monitor (TAM) (Thermometric AB, Sweden), which consisted of four independent channels. The technique has high sensitivity, being able to detect heat changes as small as  $10^{-6}$ °C. The heat flow signal ( $dQ/dt$  in mW) is monitored as a function of time. Thus, by integrating the heat flow curves at a specific time, the heat evolved or absorbed can be obtained. Each sample was accurately weighed (approximately 20 mg) in a 3 ml glass ampoule, after which a tube containing a saturated solution of sodium chloride was added to give 75% RH at 25°C. The

ampoules were sealed and temperature equilibrated for 30 min. A blank experiment was undertaken by sealing an identical ampoule and salt solution without powder present. The use of a freshly sealed blank ampoule minimises heat effects due to relaxation of the rubber stopper of the ampoule, evaporation from the salt solution and the baseline drift which is associated with environmental heat changes (Briggner et al., 1994). Experiments were carried out to investigate the percentage amorphous content in the spray dried samples by analysing the crystallisation peaks using the mean of at least three experimental runs.

## 2.4. Differential scanning calorimetry (DSC)

Differential Scanning Calorimeter (Perkin Elmer, DSC 7) was used to characterise the test samples and the reference material. The DSC sample weights were between 3.5 and 5.0 mg. Sealed aluminium pans were used and measurements were made in an atmosphere of nitrogen, with a heating rate of 20°C/min over a temperature range of 30–250°C. The instrument was calibrated using indium and the auto balance was also calibrated prior to weight measurements. At least three measurements were taken for each sample.

## 2.5. Thermogravimetric analysis (TGA)

Use of TGA (2950 Thermogravimetric Analyser, TA instruments) allowed the quantification of the lactose monohydrate content in the samples. This was achieved by analysing a derivative peak of the weight loss curve. The samples were heated over a temperature range of 30–250°C at a heating rate of 20°C/min. Four measurements for each sample were taken.

Table 1  
Parameters used to spray dry lactose at different feed concentrations

Parameters	Controls
Air flow rate (dial setting)	12
Outlet temperature (°C)	85–90
Inlet temperature (°C)	185–190
Heating rate (dial setting)	11.5
Atomiser air flow rate (Normlitter/h)	400

## 3. Results and discussion

A typical response of the spray dried material following exposure to 75% RH in the isothermal microcalorimeter is given in Fig. 1. The reference material,  $\alpha$ -lactose monohydrate was tested under

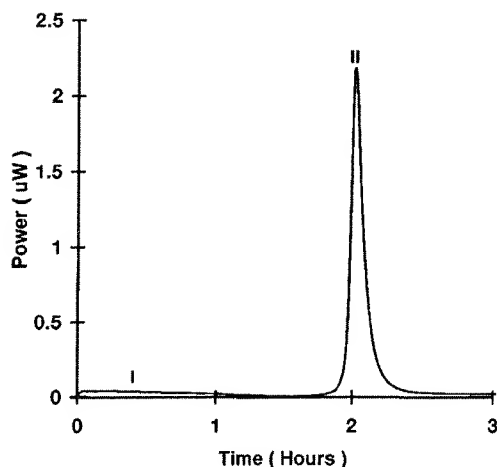


Fig. 1. A microcalorimetric trace showing an amorphous collapse peak (I) and a crystallisation peak (II) for spray dried lactose (20 g/100 ml) 20 mg at 75% RH, 25°C.

the same conditions and gave no crystallisation response, which confirmed that the material was 100% crystalline (best approximation). Two peaks are seen in Fig. 1, it was believed previously (e.g., Sebhatu et al., 1993; Briggner et al., 1994) that the first peak represented the absorption of water vapour in the amorphous structure. However, recent developments in this area of study led to the view that the first peak is more likely a heat change due to the collapse of the amorphous structure (Buckton and Darcy, 1996). This recent notion is consistent with the opinion that vaporisation and absorption have an equal and opposite response, which cancel each other. The second peak is due to the crystallisation of the amorphous lactose. The shape of the second peak demonstrates that the crystallisation process is rapid and co-operative. This co-operative process proceeded after a critical moisture concentration was reached, which was sufficient to lower the glass transition temperature ( $T_g$ ) of amorphous lactose to below the operating temperature ( $T$ ). When the  $T_g$  of the materials was lowered to  $T$  or below, increased molecular mobility facilitated crystallisation.

It was expected that the materials spray dried from a 10 g/100 ml lactose solution would be totally amorphous, as rapid evaporation would cause fast solidification thus giving the material no opportunity to crystallise. A value of 50 mJ/mg (Fig. 2) was obtained by integrating the area under the crystallisation peak for this sample. This value is consistent with that obtained elsewhere for a totally amorphous lactose sample (Briggner et al., 1994), thus this sample is regarded as amorphous.

The material spray dried from a 20 g/100 ml feed sample (which is at the equilibrium solubility of lactose at 25°C), was found to contain 91% amorphous material (obtained from the ratio of the area of the crystallisation peak to that of the amorphous sample), which was within the expected range given the possibility that some nucleation sites may remain, as this solution is approximately at equilibrium solubility.

The results for the feed containing 30 g/100 ml and the 40 g/100 ml (Table 2) samples were surprising as the measured amorphous content was higher than expected. The 30 g/100 ml sample contained about 67% of the lactose in solution with the remainder in suspension. It was expected that the percentage amorphous values would reflect the percentage lactose that was in solution. The lactose in suspension was expected to emerge from the system as either  $\alpha$ -monohydrate or anhydrous crystalline forms. However, the 30 g/100 ml feed yielded a powder with 89% amorphous content, which was substantially higher than expected. The 40 g/100 ml feed had approximately 50% of the lactose in solution and 50% in suspension. However, the calculated value for amorphous content was 82% which again is much higher than that which was dissolved in the feed material. A possible explanation for the elevated amorphous contents of the suspension feeds is that atomisation pressure in the spray nozzle may have had a milling effect on the lactose that was in suspension. This pressure dependant milling effect may have resulted in the reduction of lactose particle size giving increased apparent solu-

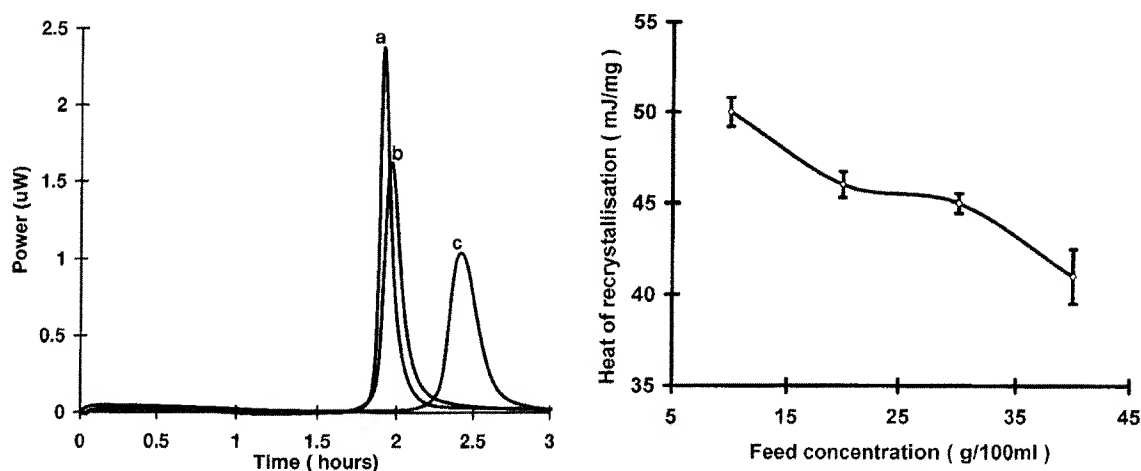


Fig. 2. (a) Typical microcalorimetric traces to show the crystallisation responses for the 40 g/100 ml (peak a), 20 g/100 ml (peak b) and 10 g/100 ml (peak c) products (30 g/100 ml trace not shown for clarity of the figure). Products with the highest amorphous content have the longest lag time prior to the crystallisation response, a plot of the mean area under the curve for each sample is given in (b). (b) A plot of mean area under the crystallisation curve (at 75%RH, 25°C) against feed concentration ( $n = 4$ , error bars represent standard deviations).

bility (Buckton and Beezer, 1992), solubility would be further influenced by the change in temperature of the feed as it passes through the spray nozzle. The effect of temperature in the nozzle affecting solubility is unlikely to be the only effect as if this explanation was totally responsible for the changes in amorphous content, then the 20 g/100 ml sample would have been expected to be totally amorphous (as it was at equilibrium solubility at 25°C), whereas it remained at 91% amorphous. It is however possible that changes in temperature in the nozzle become more significant when the suspended material load increases, perhaps due to particle–particle attrition. An alternative explanation is that inter-particle attrition and abrasion, under the influence of the atomiser centrifugal pressure, resulted in the physical disruption of the lactose crystal structure, giving a solid state transition to the amorphous form.

Changes in particle size were measured and are presented in Table 3. The feed material has a much larger size than any of the spray dried products. Based on these data some milling does take place during passage through the atomiser. The 10 g/100 ml feed produced the smallest size

product (Table 3) with the sizes for the products produced from other feeds being essentially identical (within experimental error). It can be concluded from these data that the presence of plentiful nucleation sites (which would be expected to exist in all except the 10 g/100 ml feeds) has resulted in larger particles, by allowing earlier solidification than for the material which was completely dissolved.

From the available evidence it is probable that a combination of the above explanations (solubility changes and solid state transitions) may be the reason for the unexpectedly high amorphous contents in the suspension feed products.

### 3.1. Determination of the lactose polymorphic forms present in spray dried lactose

The characterisation of polymorphs in the spray dried lactose samples was undertaken using DSC, TGA and microcalorimetry results.

From the isothermal microcalorimetry results it was established that a 10 g/100 ml sample contained 100% amorphous lactose, which meant that there was no crystalline material (best approximation) present. This observation was supported by



Table 2

Summary of the feed material and the consequent nature of the spray dried product

Feed Conc. (g/100 ml)	% in solution in feed	Amorphous in product (%)	$\alpha$ -anhydrous in product (%)	Mono-hydrate in product (%)	$\beta$ -anhydrous in product (%)
10	100	100 (1.3)	0	0	0
20	ca. 100	91 (1.3)	9 (1.4)	0	0
30	67	89 (1.0)	11 (1.0)	0	0
40	50	82 (3.3)	13 (3.1)	5 (0.3)	0

The standard deviations are in parenthesis,  $n = 4$ .

The data for  $\beta$ -lactose are open to error as they are derived from the absence of a visible melt at the appropriate point on the DSC traces. It is reasonable to assume that a small part of the anhydrous material may indeed be present as  $\beta$ -lactose, but if this is so it is below the detection limit.

the DSC trace for this sample which showed no lactose monohydrate dehydration peak in the 140–150°C temperature range (see Fig. 3 for a DSC trace for reference material) and no  $\beta$ -lactose melting peak at about 235°C. The TGA derivative curve showed no evidence of weight loss associated with hydrate water. These data supported the isothermal microcalorimetry and as such it was concluded that the 10 g/100 ml samples contained no crystalline lactose.

The product from 20 g/100 ml feed contained 91% amorphous lactose, therefore the remaining 9% could potentially consist of one or all of the lactose polymorphs. The absence of any DSC melting peak at 235°C demonstrates that there are no detectable amounts of  $\beta$ -lactose in the sample.

Table 3

The particle sizes ( $\mu$ ) of the starting  $\alpha$ -lactose monohydrate and the spray dried products produced from different feed concentrations

	10% under-size	50% under-size	90% under-size
Starting material	9.2 (3.5)	22.8 (6.0)	46.0 (11.4)
10 g/100 ml feed	3.3 (0.6)	7.2 (0.3)	16.4 (5.0)
20 g/100 ml feed	3.4 (0.2)	11.2 (0.4)	23.5 (1.1)
30 g/100 ml feed	3.5 (0.3)	12.6 (1.0)	24.6 (1.7)
40 g/100 ml feed	3.8 (0.3)	13.9 (0.2)	25.9 (0.1)

Standard deviations are in parenthesis,  $n = 4$ .

The monohydrate dehydration peak was also absent, but there was a melting peak at 216°C (Fig. 3). The TGA derivative trace showed no weight loss associated with hydrate water, which indicated that there was no detectable lactose monohydrate in the sample. It is therefore, concluded that the 20 g/100 ml sample contained no lactose monohydrate and no  $\beta$ -lactose. By reasonable deduction, the 20 g/100 ml sample was thought to contain 9% anhydrous  $\alpha$ -lactose and 91% amorphous lactose. The observed DSC peak (Fig. 3) was in keeping with the literature value of 216°C for anhydrous lactose (Lerk, 1983). The 30 g/100 ml sample was found to contain 89% amorphous lactose and 11% anhydrous  $\alpha$ -lactose using a similar logic. It should be noted, however, that the absence of a melting peak on the DSC does not prove total absence of the  $\beta$ -lactose as there is a certain threshold quantity required to allow detection, as such the above estimates are best approximations.

The 40 g/100 ml sample, showed a TGA secondary weight loss derivative peak (see Fig. 4), which was consistent with the lactose monohydrate reference material. The derivative peak represented a loss of 0.0355 mg of water ( $0.0355 \times 10^{-3}/18$  moles of water). This number of moles was equivalent to the number of moles lactose monohydrate (1:1 molar ratio). The % lactose monohydrate content was then expressed as a % weight of the analysed sample. The lactose monohydrate content in the 40 g/100 ml sample was calculated to be approximately 5%. However, the dehydration peak was not visible on the DSC

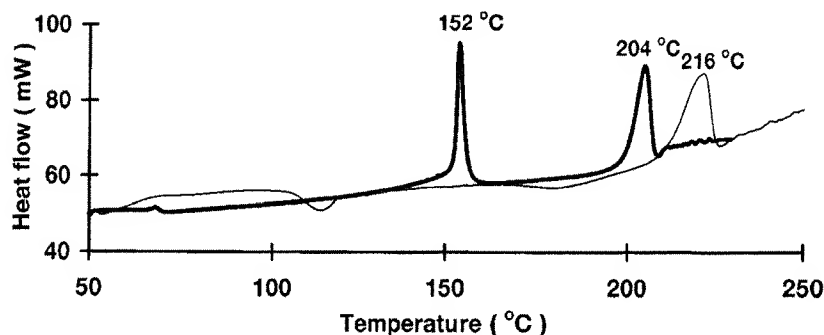


Fig. 3. A DSC trace for lactose monohydrate (reference material) showing a dehydration peak (152°C) and melting peak (204°C) (Bold line) and a typical scan for spray dried lactose (20 g/100 ml) showing the absence of  $\beta$ -lactose melting peak and no lactose monohydrate dehydration peak (however a  $T_g$  is seen as a baseline disruption at ca 120°C and a melt at 216°C is observed).

trace for the sample, this may be due to the low sensitivity of the DSC to detect the presence of small amounts of lactose monohydrate (Angberg et al., 1991). The DSC trace for this material also showed no  $\beta$ -lactose melting peak and exhibited a melting peak at 216°C, which could represent the melting peak for either lactose monohydrate and anhydrous lactose. Based on the evidence available it is concluded that the material obtained from the 40 g/100 ml feed consisted of 5% lactose monohydrate, 82% amorphous lactose and about 13% anhydrous lactose. The presence of lactose monohydrate in this sample may be due to the high feed rates which were necessary to control the outlet temperature. The feed rates for the

other samples were comparatively low, therefore, in the other samples it would have been easier for lactose to be dehydrated to form anhydrous lactose.

Whilst it should be remembered that the accuracy of the thermal analysis means that small amounts of other polymorphs will not have been detected, clear differences in the physical form are observed depending upon the feed concentration, these differences are summarised in Table 2. Substantial differences in product are possible depending upon both spray drying conditions and the concentration of the feed material.

#### 4. Conclusion

The concentration of feed material was found to have a significant effect on the properties of the spray dried materials. An increase in lactose content in the feed solution or suspension in the more concentrated preparations resulted in a decrease in percentage amorphous lactose in the spray dried products. Under the conditions used, the lactose in solution solidified in an amorphous state. However, at higher feed contents it was observed that suspended lactose was also converted from crystalline to amorphous material. Processes in the atomiser, followed by rapid solidification, cause the lactose in suspension to become amorphous through solid or liquid transitions or more likely a combination of both. At

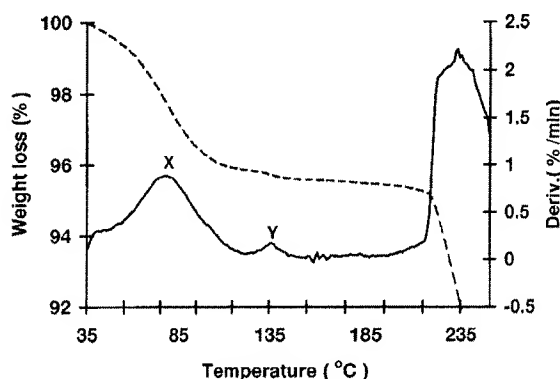


Fig. 4. TGA weight loss curve for spray dried lactose (40 g/100 ml) showing a derivative peak corresponding to loss of absorbed (X) and hydrate (Y) water.

higher feed solids incomplete dehydration of the suspended lactose particles may occur, which may result in some lactose monohydrate in the products.

By selecting the appropriate feed concentrations spray dried lactose can be manufactured with various polymorphic proportions which suit the desired tableting properties.

### Acknowledgements

This work was funded by EPSRC and Smithkline Beecham (Great Burgh, Epsom, UK) to whom we are grateful.

### References

- Angberg, M., Nystrom, C., Castensson, S., 1991. Evaluation of heat-conduction microcalorimetry in pharmaceutical stability studies III. Crystallographic changes due to water vapour uptake in anhydrous lactose powder. *Int. J. Pharm.* 73, 209–220.
- Briggner, L.-E., Buckton, G., Bystrom, K., Darcy, P., 1994. The use of isothermal microcalorimetry in the study of changes in crystallinity induced during the processing of powders. *Int. J. Pharm.* 105, 125–135.
- Buckton, G., Beezer, A.E., 1992. The relationship between particle size and solubility. *Int. J. Pharm.* 82, R7–R10.
- Buckton, G., Darcy, P., MacKellar, A.J., 1995. The use of isothermal microcalorimetry in the study of small degrees of amorphous content of powders. *Int. J. Pharm.* 117, 253–256.
- Buckton, G., Darcy, P., 1996. Water mobility in amorphous lactose below and close to the glass transition temperature. *Int. J. Pharm.* 136, 141–146.
- Hancock, B.C., Shamblin, S.L., Zografi, G., 1995. Molecular mobility of amorphous pharmaceutical solids below their glass transition temperatures. *Pharm. Res.* 12, 799–806.
- Lerk, C.F., 1983. Physico-chemical properties of lactose. *Proceedings of the 22nd International Colloquium on Industrial Pharmacy*, Ghent, pp. 59–89.
- Masters, K., 1990. *Spray Drying Handbook*, Longman, New York.
- Sebhatu, T., Angberg, M., Ahlneck, C., 1993. Assessment of the degree of disorder in crystalline solids by isothermal microcalorimetry. *Int. J. Pharm.* 104, 135–144.
- Van Scoik, K.G., Carstensen, J.T., 1990. Nucleation phenomena in amorphous sucrose systems. *Int. J. Pharm.* 58, 185–196.
- Vromans, H., Bolhuis, G.K., Lerk, C.F., van de Biggelaar, H., Bosch, H., 1986. Studies on the tableting properties of lactose. VII. The effect of variations in primary particle size and percentage of amorphous lactose in spray dried lactose products. *Int. J. Pharm.* 35, 29–37.

PHYSICOCHEMICAL PROPERTIES OF SPRAY DRIED DRUGS:  
PHENOBARBITONE AND HYDROFLUMETHIAZIDE

O.I. Corrigan, K. Sabra and E.M. Holohan  
Department of Pharmaceutics, School of Pharmacy,  
Trinity College, 18 Shrewsbury Road, Dublin 4,  
Ireland.

ABSTRACT

The potential of spray drying to produce high energy drug forms was investigated using phenobarbitone and hydroflumethiazide. Whereas commercial phenobarbitone is normally Form II, the product produced by spray drying had a large specific surface area ( $17\text{m}^2/\text{g}$ ) and physical properties similar to Form III. The apparent solubility of this spray dried material was 25% greater than that of Form II. An amorphous product was obtained on spray drying phenobarbitone with 10% PVP. Spray dried hydroflumethiazide was amorphous and had an apparent solubility 1.61 times that of the crystalline form. Co-spray drying hydroflumethiazide with 10% PVP also produced an amorphous system. Differential scanning calorimetry suggested that the system contained both amorphous drug and an amorphous drug-PVP complex. The product had an apparent solubility 2.5 times that of the pure crystalline drug. Spray drying, either in the presence or absence of excipients, can result in the formation of high energy drug polymorphs or amorphous phases not normally obtained by conventional precipitation procedures.

INTRODUCTION

Spray drying and spray dried products have been used in the production of pharmaceuticals for many years (1). The process has been used to dry heat sensitive drugs and to produce free flowing microparticles which may be used in the manufacture of conventional (2) and sustained action dosage forms (3). Microencapsulated products have also been prepared by spray drying techniques (4, 5, 6).

The application of spray drying to alter the biopharmaceutical properties of individual drugs has been less widely studied, given

the influence drug solid state properties may have on bioavailability (7, 8). Specifically, drug particle size, degree of crystallinity and polymorphic form may frequently alter drug dissolution and hence bioavailability. The use of spray drying to achieve micronization and improved dissolution of a poorly water soluble quinazolinone compound has been documented (9). Sodium salicylate (10) and sulfamethoxazole (6,11) when spray dried with excipients resulted in alteration of the crystal form of the drug, either to a different polymorphic form or to an amorphous phase. Indeed spray dried lactose has been reported to be a mixture of three forms: the  $\alpha$ -monohydrate,  $\alpha$ -anhydrous and  $\beta$ -anhydrous (12). More recently a number of  $\beta$ -lactam antibiotics (13) were spray-dried in the absence of excipients and produced energy rich drug forms.

In this communication the authors investigate the potential of spray drying to enhance biopharmaceutically relevant properties of specific drugs. The preparation and properties of spray dried phenobarbitone and hydroflumethiazide are discussed. Pheno-barbitone was chosen since it has been reported to exist in many crystalline modifications as well as a glass form (14, 15). In contrast, hydroflumethiazide has not been reported to exhibit true polymorphism but forms a solvate with ethanol (16) and a high energy amorphous phase in some polyvinylpyrrolidone (PVP) containing coprecipitates (20).

#### MATERIALS AND METHODS

##### Preparation of Spray Dried Samples

Materials to be spray dried were dissolved in a suitable alcoholic or aqueous-alcoholic solvent. The solution was dried using a Buchi Minispray 190 spray drier. Except where indicated otherwise, the inlet and outlet temperatures were in the ranges 130-140°C and 93-100°C respectively. Feed inputs in the range 0.5 - 1.0 L. hr<sup>-1</sup> were employed. Anhydrous phenobarbitone (Form II) was initially prepared from phenobarbitone sodium as previously described (17) and sieved to a fine powder (180  $\mu$ m sieve). Hydroflumethiazide B.P. was used without further purification.

##### X-ray Diffraction and Infra-red Analysis.

X-ray diffraction patterns were obtained on powder samples using nickel filtered copper radiation. Both the K Br disc and Nujol mull methods were used for infra-red analysis.

### Differential Scanning Calorimetry (DSC)

Samples, 2 - 4 mg, were examined using a Perkin Elmer Model DSC 1B instrument at a scanning speed of  $16^{\circ} \text{ min}^{-1}$ .

### Microscopy

Photomicrographs of spray dried particles were obtained using a Jeol J S M - T200 Scanning Electron Microscope. Samples were also examined with a hot stage microscope.

### Surface Area Measurement

The specific surface area of powder samples was determined using a BET gas adsorption apparatus (Micromeritics Instrument Corporation, Atlanta, U.S.A. Model 220/42801 P/N). Sample weights in the range 0.4 to 1.5 G and  $\text{N}_2$  were employed.

### Solubility and Dissolution Rate

Solubilities were determined (a) from excess samples of drug equilibrated on a shaker bath at  $37^{\circ}\text{C}$  for 24 hrs and (b) in conical flasks stirred at 300 r.p.m. (18, 19) for 2 to 3 hours. Apparent solubilities of metastable systems were also determined in media containing 1% PVP (Plasdone C-15) in order to inhibit transformation of the metastable phase. When the inclusion of PVP failed to inhibit the transformation completely, further additions of the metastable form were made to the solution medium in order to establish the maximum apparent solubility of the unstable form.

Dissolution profiles were determined from compressed discs of drug mounted in paraffin wax as previously described (20). Both phenobarbitone (17) and hydroflumethiazide (20) were assayed by UV spectroscopy as previously described. A correction to the absorbance for phenobarbitone was necessary in systems containing PVP.

## RESULTS AND DISCUSSION

### Phenobarbitone

Scanning electron micrographs of spray dried phenobarbitone are compared to the non spray dried material in Fig. I. Spray drying produced spherical particles of  $3 \mu\text{m}$  in diameter which formed fairly uniformly sized particle aggregates of  $8 \mu\text{m}$  in diameter. These powders exhibited a large specific surface of  $16.9 \text{ m}^2 \text{ g}^{-1}$  by the gas adsorption method.

X-ray diffraction (Fig. 2), DSC (Fig. 3) and infra-red data indicate a change in crystal form on spray drying, the form produced

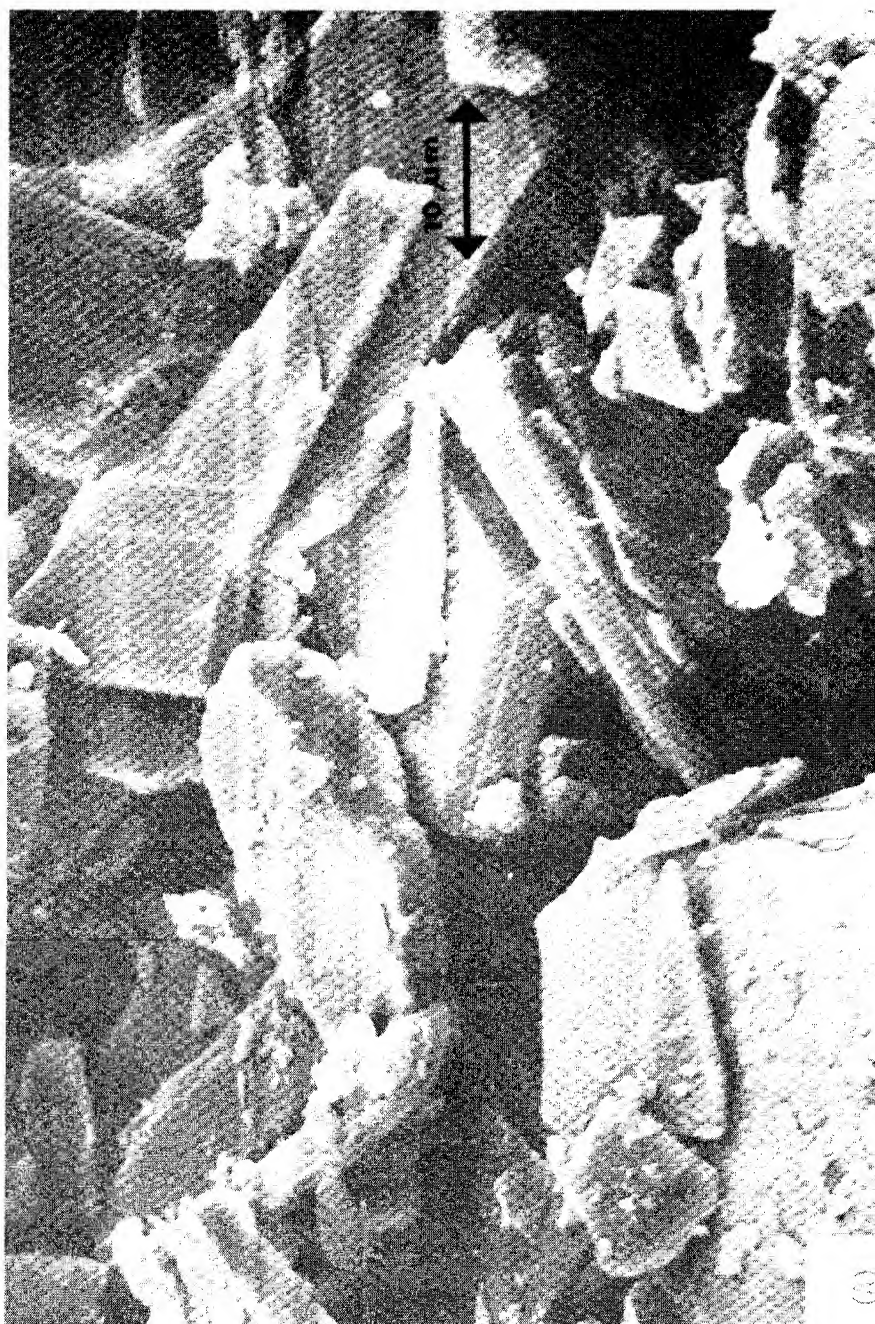


Fig. 1A. Electron photo-micrograph of phenobarbitone, non spray dried.

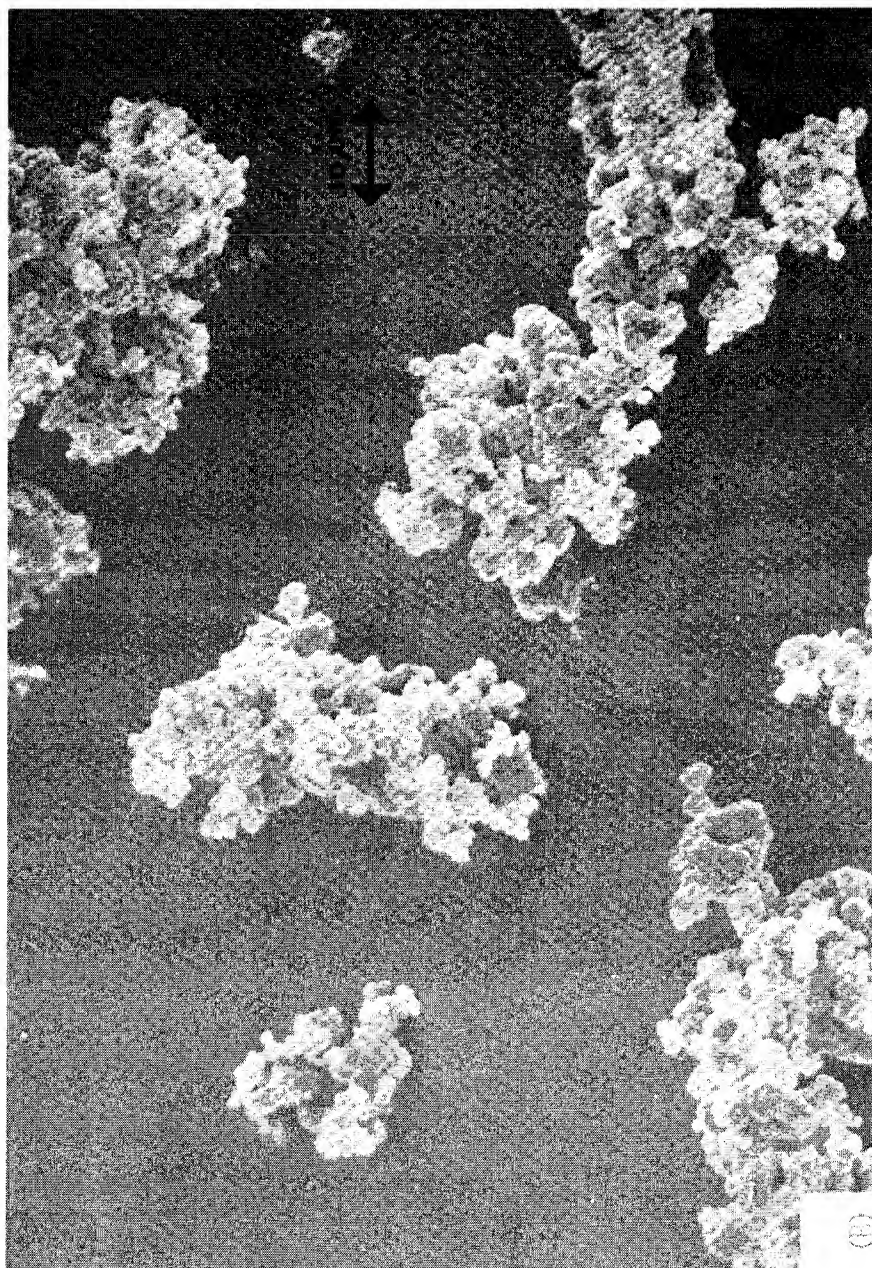


Fig. 1B. Electron photo-micrographs of phenobarbitone spray dried, sample A.



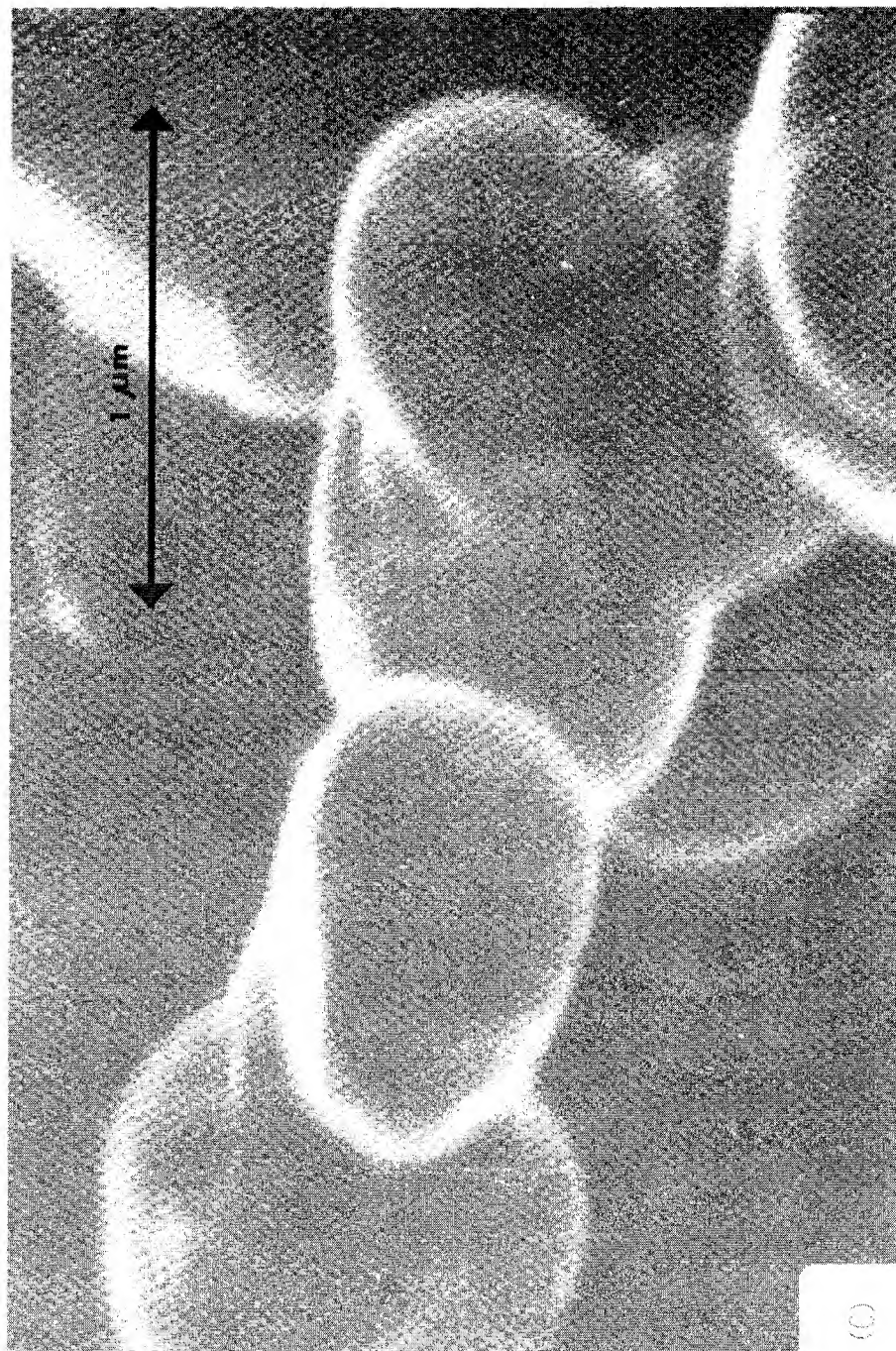


Fig. 1C. Electron photo-micrograph of phenobarbitone, spray dried.

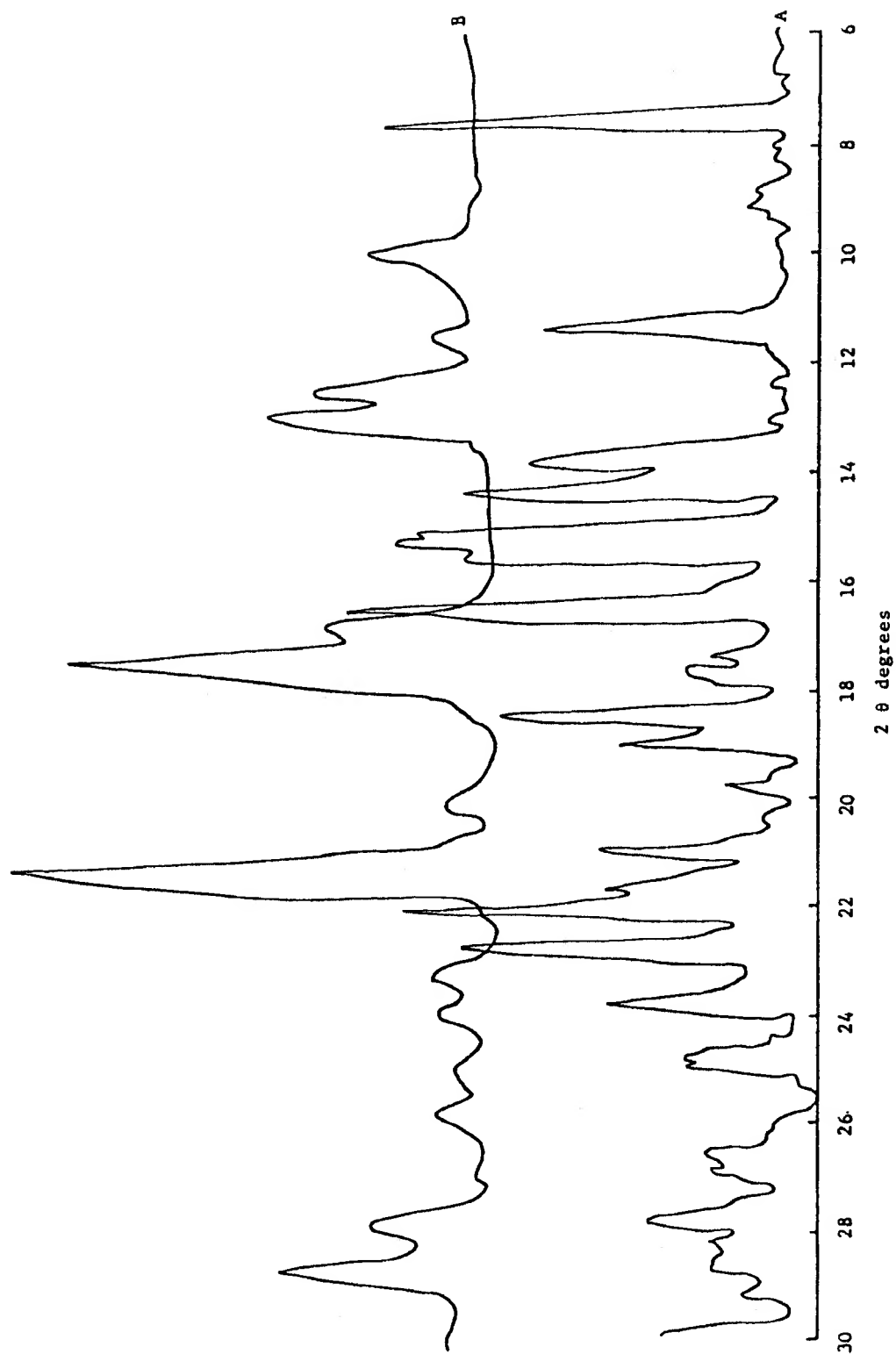


FIGURE 2

X-ray diffraction patterns for phenobarbitone samples - A, Non spray dried; B, Spray dried.

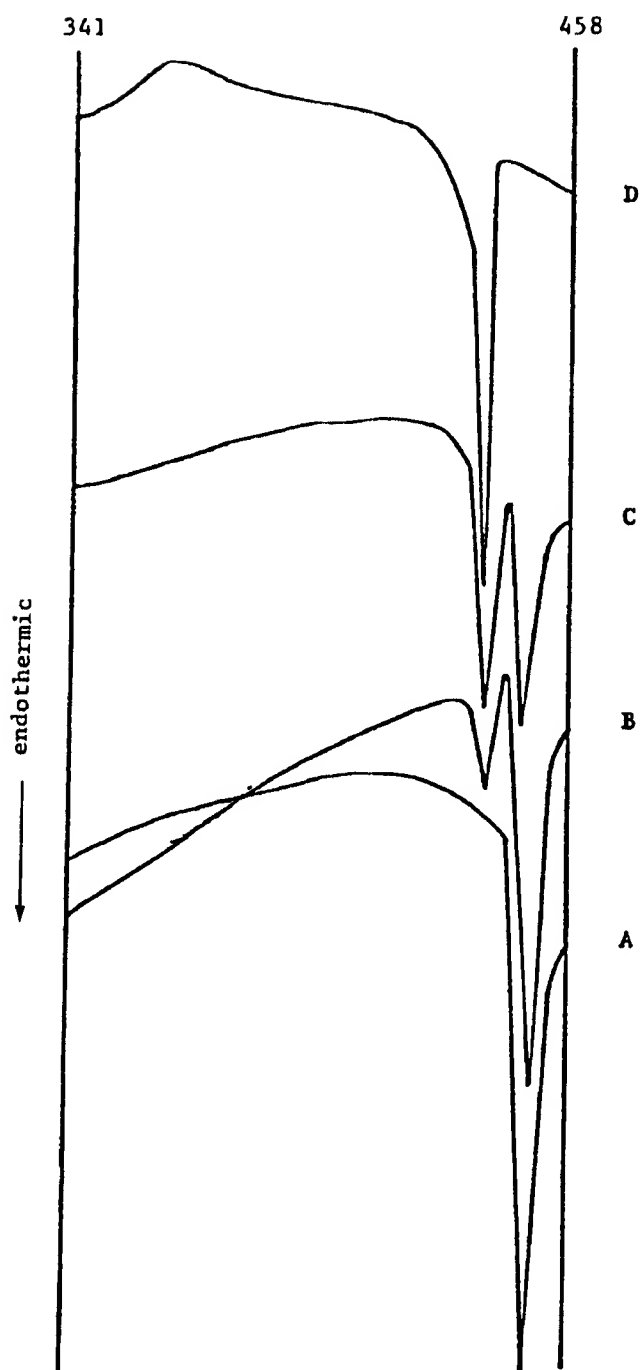


FIGURE 3

DSC thermograms of phenobarbitone samples ( $^{\circ}\text{K}$ )

A, non spray dried; B, spray dried at spray flow rate of  $750 \text{ Nl.h}^{-1}$ ; C, spray dried at spray flow rate of  $200 \text{ Nl.h}^{-1}$ ; D, spray dried from 10% PVP solution.

being similar in characteristics to Form III. Commercial phenobarbitone generally consists of Form II (21, 22) and it has been suggested (21) that Form III could not be obtained by precipitation.

Attempts were made to generate other forms by altering the spray drying conditions. Changing the solvent to water or ethanol-water mixtures still resulted in Form III. Similarly, changing the degree of solvent saturation, feed input rate or the temperature gradient (inlet range 150-80°C and outlet range 95-60°C respectively) did not alter the crystal form. Increasing the spray flow rate from 200 Nl.h<sup>-1</sup> to 750 Nl.h<sup>-1</sup> resulted in a systematic decrease in the size of the first DSC endotherm (Fig. 3). However, as no significant change in X-ray diffraction pattern was observed, the possibility that a change either in crystal form or the formation of a mixture of two forms can be excluded. Neither were significant changes evident from light or electron microscopy. Reilly (21) has previously reported that phenobarbitone phase transition rates are dependent on the method of sample preparation, while lattice disorder induced by the method of preparation has been reported to reduce the heat of fusion of sulphathiazole (23). Either of these effects may explain the quantitative changes observed in the DSC thermograms with changing spray flow rate.

Solubility profiles at 37°C of spray dried and non spray dried phenobarbitone are shown in Fig 4. The spray dried drug had the higher initial solubility but converted to a more stable form. Solubilities were therefore determined in media containing 1% PVP, a polymer known to retard the crystal transformation of a number of compounds which occur in aqueous media (16, 24). The presence of PVP retarded the transformation of spray dried phenobarbitone and also seemed to slow the rate of equilibration of the non spray dried sample (Fig. 4). These results suggest that the spray dried form has a solubility at 37°C which is 1.24 times that of Form II.

The dissolution profile obtained from compressed discs of constant surface area (in isotonic buffer pH 5.3 at 37°C containing 1% PVP) is compared to that of the non spray dried form in Fig. 5. Compression did not effect conversion of the spray dried material to Form II although some decrease in the area of the first DSC endotherm was evident on DSC scans of disc fragments. The difference

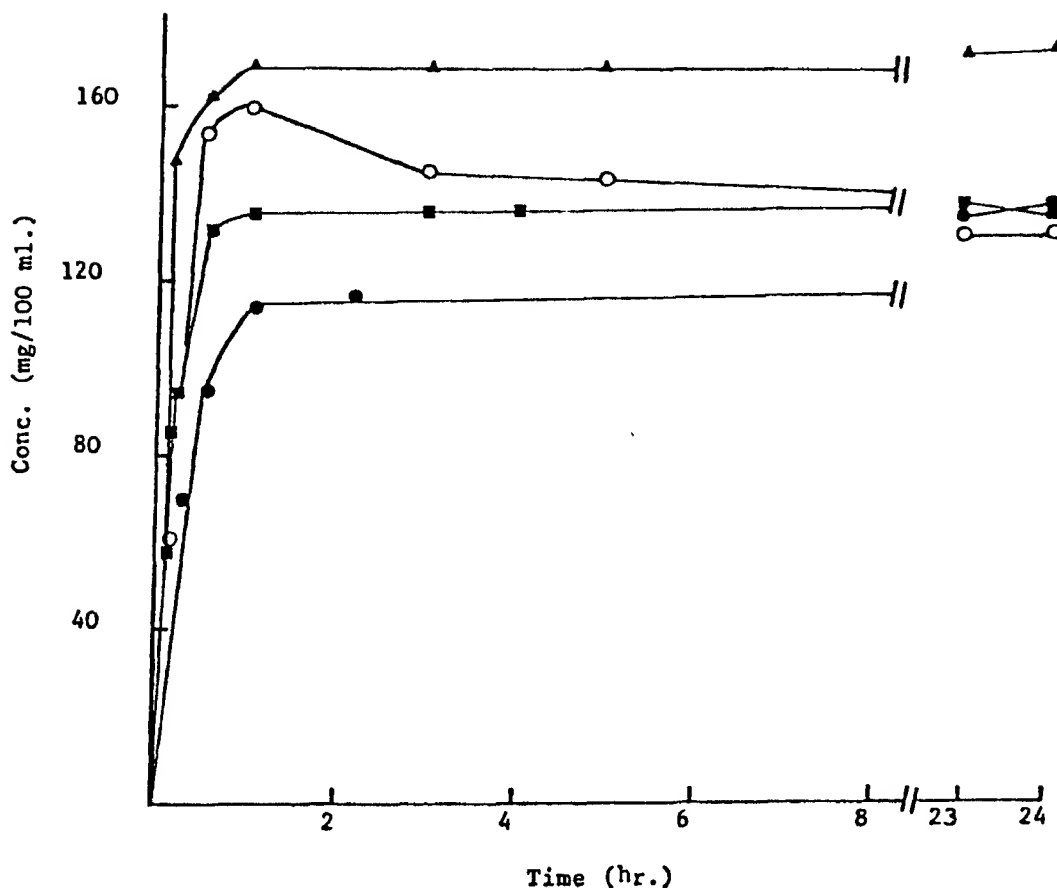


FIGURE 4

Solubility profiles of phenobarbitone samples at 37°C.

- (■) Non spray dried at pH 5.3; (○) spray dried at pH 5.3;
- (●) Non spray dried in media containing 1% PVP;
- (▲) Spray dried in media containing 1% PVP.

in dissolution profiles are consistent with the solubility data, the spray dried material having the higher dissolution rate. The inclusion of PVP in the dissolution medium, however, resulted in a lower dissolution rate for the non spray dried drug than previously observed in the absence of PVP (17). In the absence of PVP no difference in dissolution between the two forms was detected.

Previous reports have shown that phenobarbitone Form II is metastable in aqueous media (25, 26) converting to a hydrate (Form XIII).

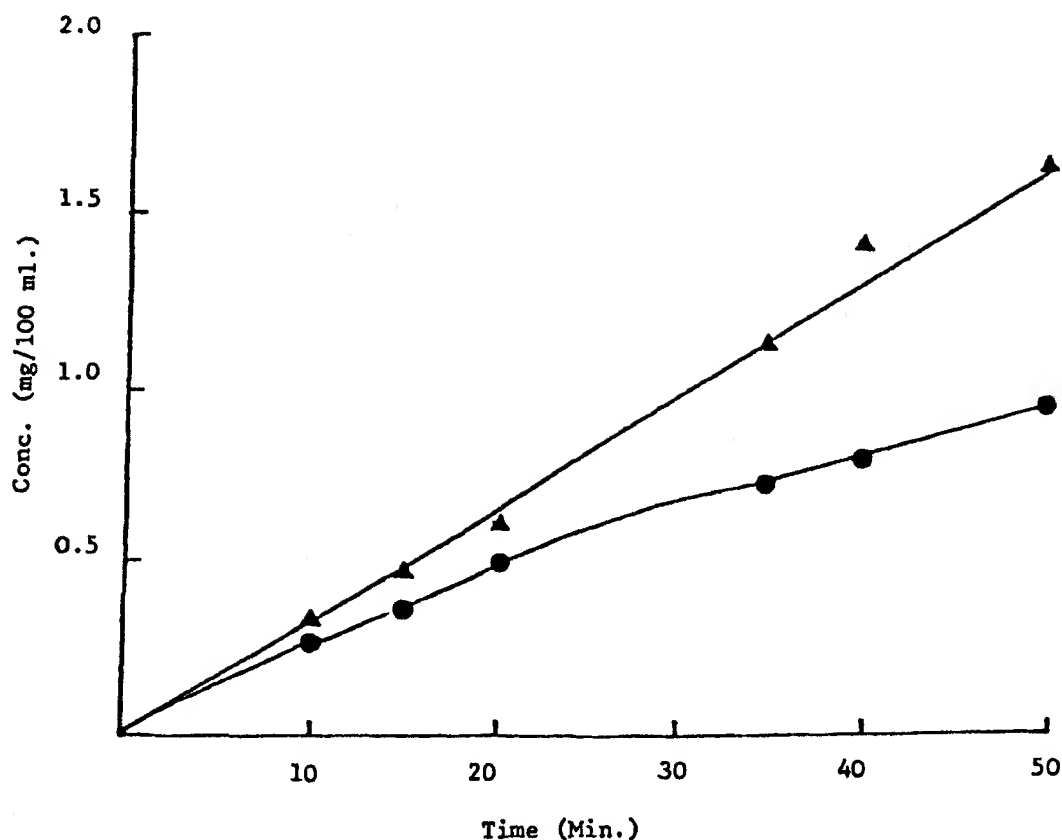


FIGURE 5

Dissolution profiles of phenobarbitone samples at 37° in isotonic phosphate buffer pH 5.3 containing 1% PVP. (●) Non spray dried; (▲) spray dried.

The transition temperature of these two forms is about 37°C and therefore evidence of this transition was not apparent from the solubility profiles in the current work.

Using a tape dissolution method, Clements and Stanski (22) examined the dissolution properties of a number of polymorphic forms of phenobarbitone. They observed that Form III dissolved 28% faster than Form II in purified water, a finding consistent with the difference detected in the current work.

The high energy form of phenobarbitone produced on spray drying seems quite stable as no change in physical properties occurred up to 9 months.



Fig. 6A. Electron photo-micrographs of hydroflumethiazide non spray dried.

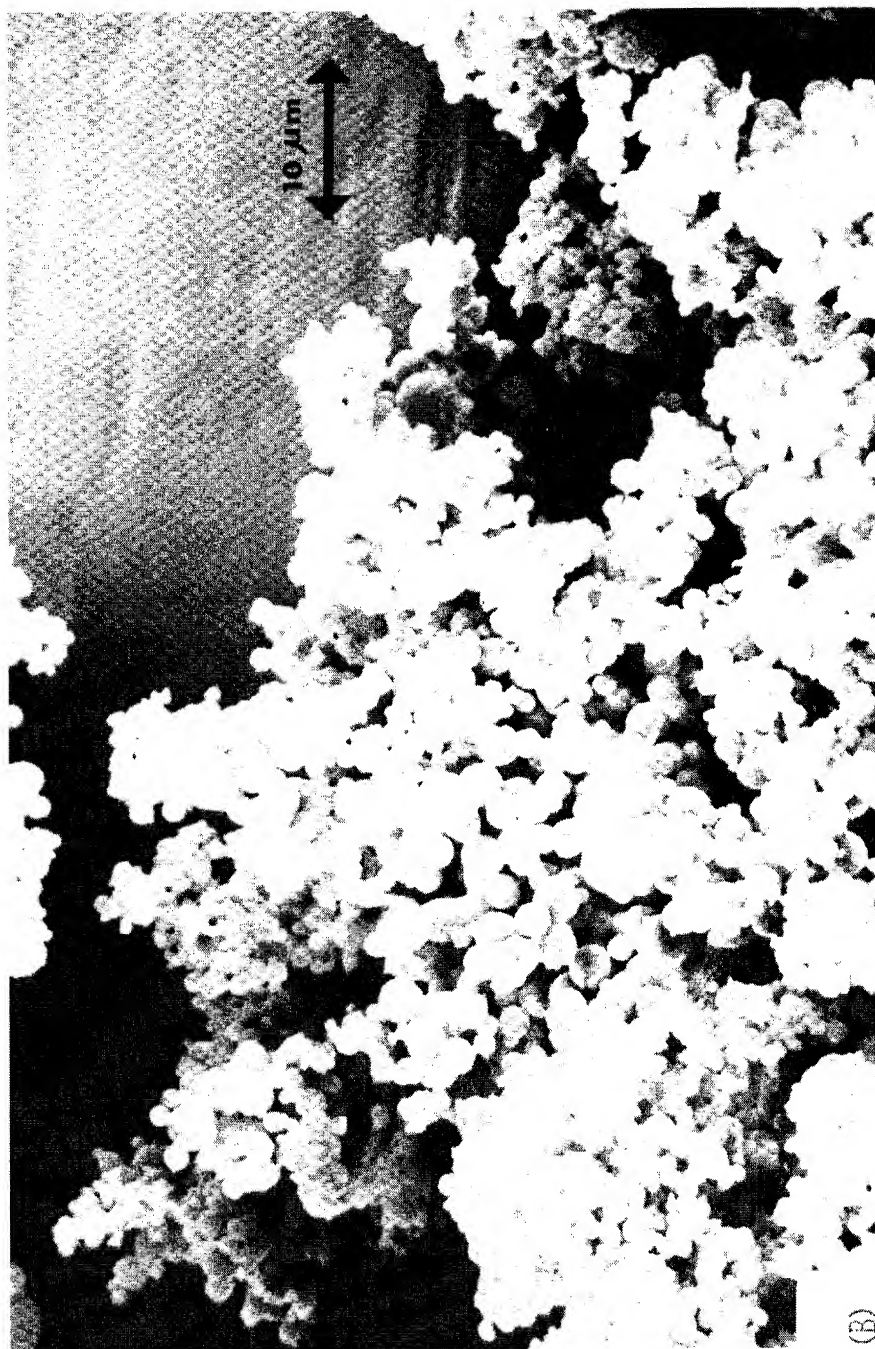


Fig. 6B. Electron photo-micrographs of hydroflumethiazide Spray dried.



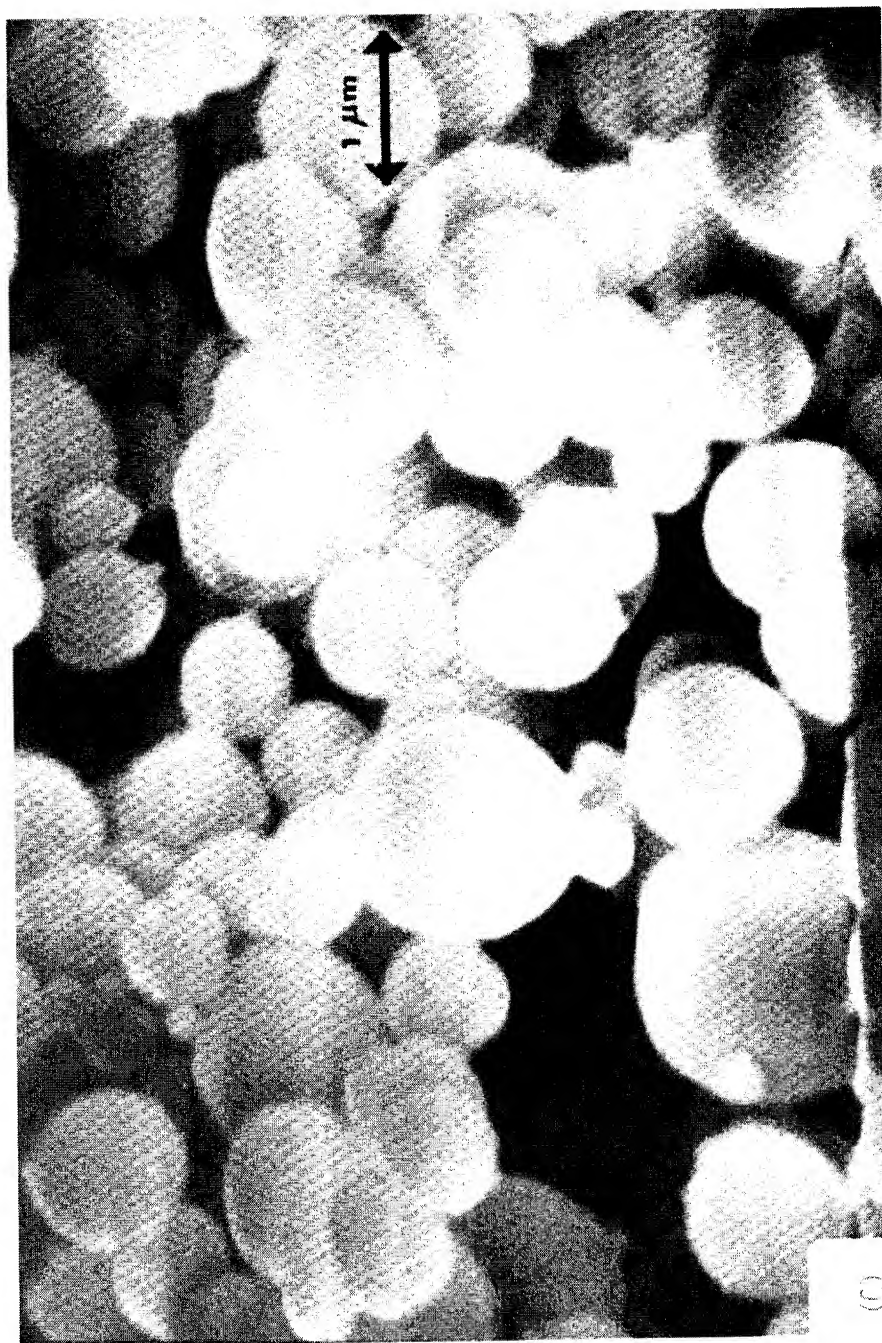


Fig. 6C. Electron photo-micrographs of hydroflumethiazide C spray dried.

Hydroflumethiazide

Scanning electron micrographs of spray dried hydroflumethiazide and non spray dried drug are shown in Fig. 6. The spray dried material consists of spherical particles of  $< 5\mu\text{m}$  approximately with a specific surface area of  $14.7\text{ m}^2\text{g}^{-1}$ . The X-ray diffraction patterns of the samples are compared in Fig. 7 and indicate that spray dried hydroflumethiazide is amorphous. The DSC thermogram of the spray dried drug differed from that of the normal crystalline form in the occurrence of an exothermic peak at  $135^\circ\text{C}$  (Fig. 8). Such exothermic-endothermic profiles are typical of amorphous or glassy forms (19,27). The amorphous phase of hydroflumethiazide was unstable at room temperature and converted to the more stable crystalline form in about 12 days. Thus spray drying of hydroflumethiazide from alcoholic media produces an amorphous drug form. In contrast, the rapid precipitation of hydroflumethiazide by conventional methods from ethanol, has been reported previously to produce an alcoholate (16).

The solubility profiles for spray dried hydroflumethiazide in 0.1 N HCl at  $37^\circ\text{C}$  in the presence and absence of 1% PVP are compared to the corresponding profiles for the crystalline drug in Fig. 9. In aqueous media, the amorphous phase is unstable converting rapidly to the crystalline phase in the absence of PVP. The apparent solubility of the unstable amorphous phase was estimated to be 1.61 times that of the crystalline form. Attempts to determine the intrinsic dissolution rate of this form were unsuccessful because of the brittle nature of the glassy discs produced on compression.

The existence of an amorphous phase of hydroflumethiazide was previously (20) suggested from studies of the properties of hydroflumethiazide-PVP coprecipitates. This phase was present in coprecipitates containing greater than 35% PVP (20) and dissolution experiments suggested that it had a solubility 4-5 times that of the crystalline drug. A similar difference in apparent solubility between an amorphous drug phase present in a PVP coprecipitate and that in a pure drug melt has also been reported for sulphathiazole (28).

Spray Drying with PVP

Since the spray drying of drugs in the presence of excipients has been reported to alter the solid state properties of drugs,

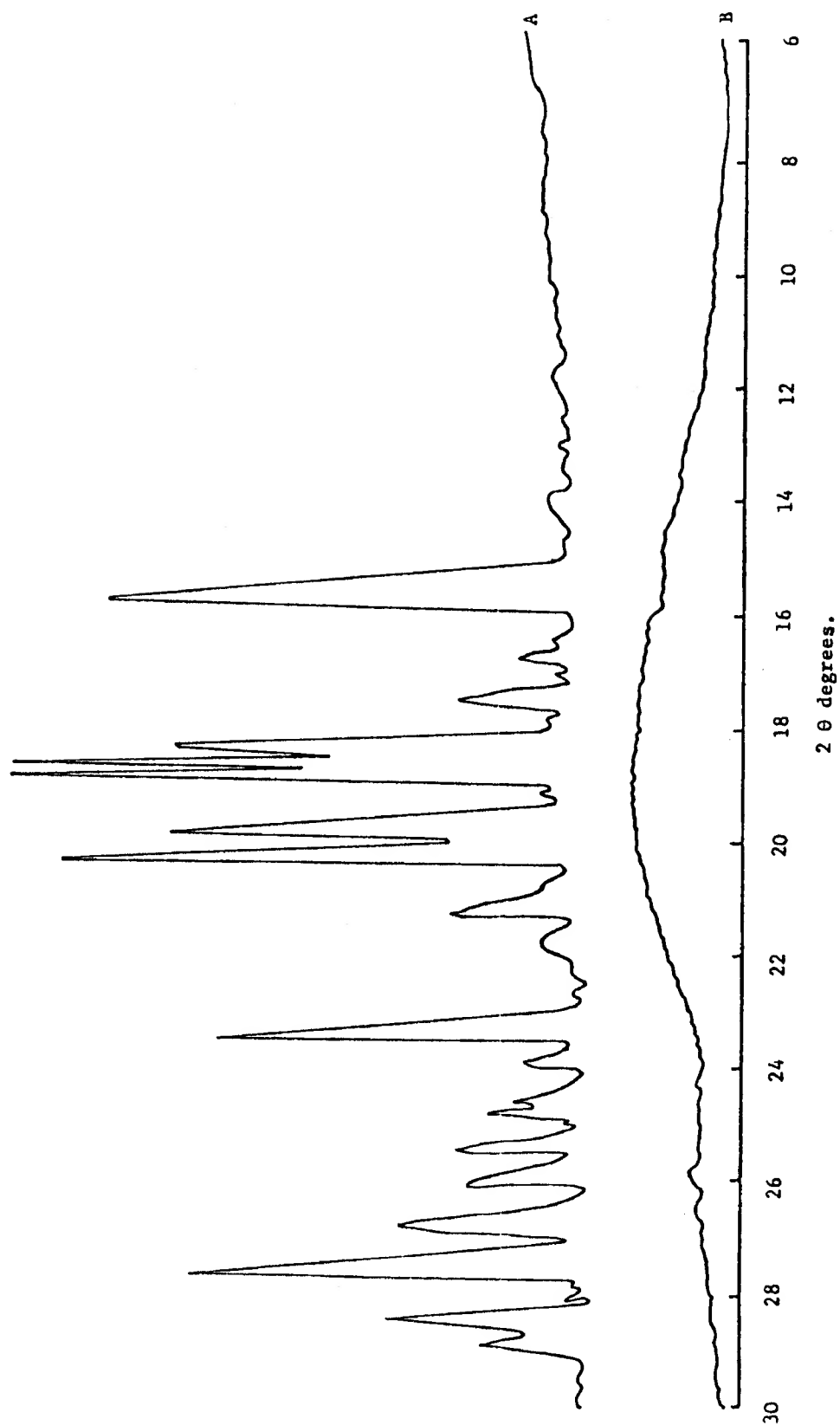


FIGURE 7

X-ray diffraction patterns for hydroflumethiazide samples - A, Non spray dried; B, Spray dried.

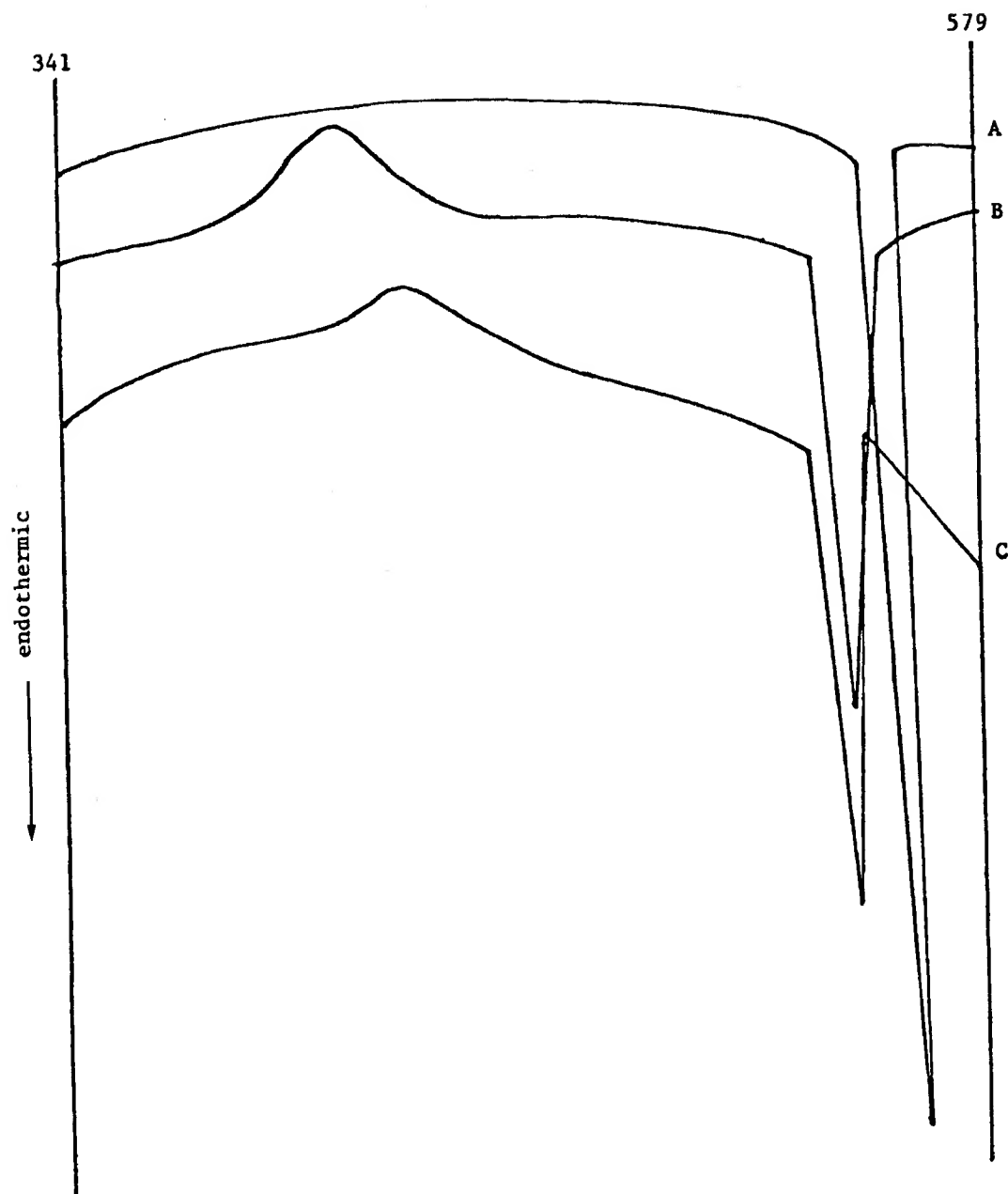


FIGURE 8

DSC thermograms of hydroflumethiazide samples ( $^{\circ}\text{K}$ )

A, non spray dried; B, spray dried; C, spray dried from 10% PVP solution.

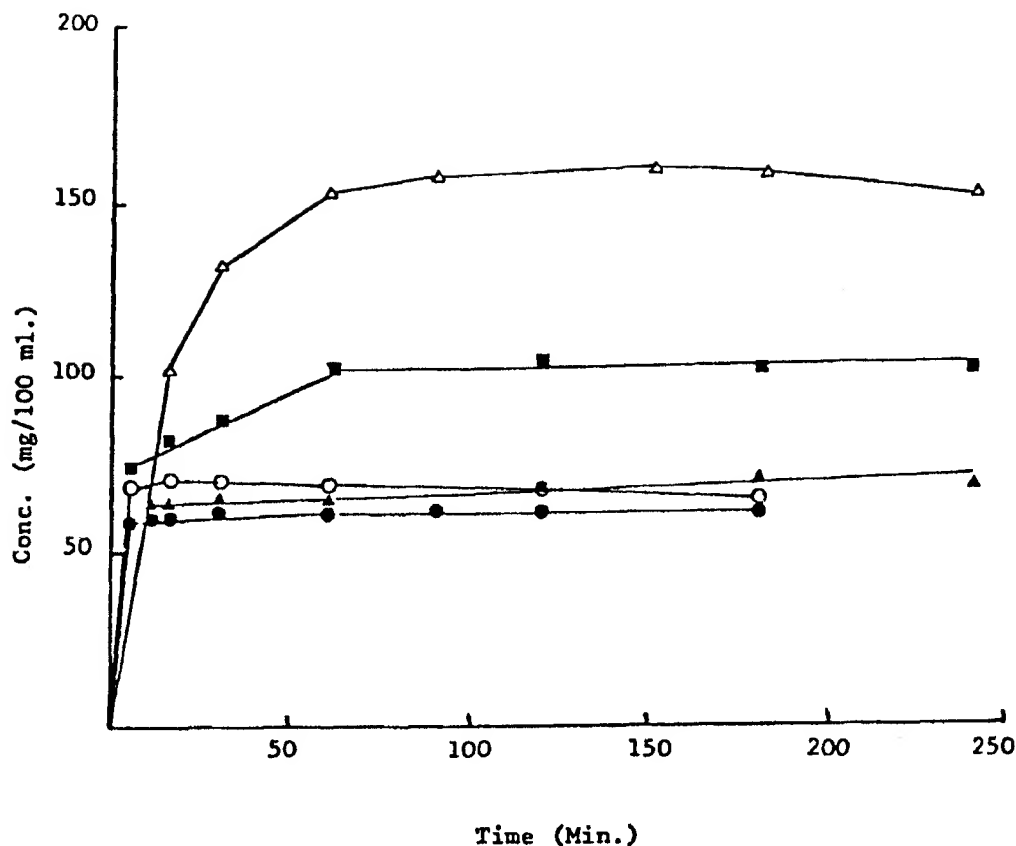


FIGURE 9

Solubility profiles of hydroflumethiazide samples at 37°

(●) Non spray dried and (○) spray dried in 0.1 NHCl media.  
(▲) Non spray dried and (■) spray dried in a media containing 1% PVP. (Δ) Spray dried from 10% PVP solution in a media containing 1% PVP.

hydroflumethiazide was therefore spray dried in the presence of low concentrations of PVP. The spray dried materials thus produced were also shown to be amorphous on X-ray analysis. As the concentration of PVP present in the spray dried solid increased, changes occurred in the DSC profiles. The exothermic peak decreased in size and moved to a higher temperature while the endothermic peak decreased and shifted to a lower temperature

(Fig. 8). Amorphous hydroflumethiazide-PVP systems can therefore be prepared by spray drying at much lower PVP weight fractions than those obtained on coprecipitation (20) and these systems appear to contain both amorphous drug and amorphous drug-PVP complex.

The solubility profile of a spray dried hydroflumethiazide system containing 10% PVP is included in Fig. 9. The solubility of this system was higher than that of the pure amorphous material being 2.5 times that of the crystalline drug. Whether this increase in solubility results from the formation of a pure hydroflumethiazide amorphous phase with a higher thermodynamic activity than the pure spray dried form, or from a hydroflumethiazide-PVP complex is unclear and currently under investigation.

Phenobarbitone is known to exist in a glass form (15) although we could not produce such a form by spray drying pure solutions of phenobarbitone. Therefore alcoholic solutions of phenobarbitone were spray dried in the presence of increasing amounts of PVP. The DSC scan for the system containing 10% PVP is included in Fig. 3. The presence of an exothermic peak suggested that the material was amorphous.

In conclusion, our experience with phenobarbitone and hydroflumethiazide has demonstrated that, in addition to changes in the micromeritic properties of a drug, spray drying, either in the presence or absence of excipients, can result in the formation of high energy drug polymorphs and/or amorphous phases not normally obtained by conventional precipitation procedures.

#### ACKNOWLEDGMENTS

This work was supported by a National Board for Science and Technology Grant (Higher Education - Industrial Cooperation Scheme) number 29/80 and Elan Corporation Ltd., Athlone, Ireland.

The authors also wish to thank G.A.F. (Great Britain) Ltd. for the Plasdone C-15 used in the project, Dr. C.J. Stillman, Geology Department, Trinity College Dublin, for X-ray diffraction facilities and Mr. D. Simpson, Microelectronics and Electrical Engineering Department, for the Scanning Electron Micrographs.

#### REFERENCES

1. J.M. Newton, Mfg. Chemist Aerosol News, 37, 33 (1966).
2. W.C. Gunsel and L. Lachman, J. Pharm. Sci., 52, 178 (1963).

3. S.S. Kornblum, J. Pharm. Sci., 58, 125 (1969)
4. C. Voellmy, P. Speiser and M. Soliva, J. Pharm. Sci., 66, 631 (1977).
5. Y. Kawashima and H. Takenaka, J. Pharm. Sci., 63, 1546 (1974).
6. H. Takenaka, Y. Kawashima and S-Y. Lin., J. Pharm. Sci., 69, 1388 (1980).
7. J. Haleblan and W. McCrone, J. Pharm. Sci., 58, 911 (1969).
8. J.K. Haleblan, J. Pharm. Sci., 64, 1269 (1975).
9. S.S. Kornblum and J.O. Hirschorn, J. Pharm. Sci., 59, 606 (1970).
10. Y. Kawashima, K. Matsuda and H. Takenaka, J. Pharm. Pharmac., 24, 505 (1972).
11. H. Takenaka, Y. Kawashima and S-Y. Lin, J. Pharm. Sci., 70, 1256 (1981).
12. J.T. Fell and J.M. Newton, Pharm. Acta Helv., 45, 520 (1970).
13. M.J. Pikal, A.L. Lukes, J.E. Lang and K. Gains, J. Pharm. Sci., 67, 767 (1978)
14. R.J. Mesley, R.L. Clements, B. Flaherty and K. Goodhead, J. Pharm. Pharmac., 20, 329 (1968).
15. M.P. Summers, J. Pharm. Sci., 67, 1606 (1978).
16. O.I. Corrigan and R.F. Timoney, J. Pharm. Pharmac., 26, 838. (1974).
17. O.I. Corrigan and C.T. Stanley, Pharm. Acta Helv., 56, 204 (1981).
18. E. Shefter and T. Higuchi, J. Pharm. Sci., 52, 781 (1963).
19. W.L. Chiou and L.E. Kyle, J. Pharm. Sci., 68, 1224 (1979).
20. O.I. Corrigan and R.F. Timoney, J. Pharm. Pharmac., 27, 759 (1975).
21. G.S. Riley in "Particle Growth in Suspensions", A.L. Smith, eds., Academic Press 1973 p. 267.
22. J.A. Clements and D. Stanski, Can. J. Pharm. Sci., 6, 9 (1971).
23. K. Sekiguchi, K. Shirotani, H. Yuasa, E. Suzuki and F. Nakagawa, Chem. Pharm. Bull., 28, 3203 (1980).
24. A.R. Ebian, M.A. Moustafa, S.A. Khalil and M.M. Motawi, J. Pharm. Pharmac., 25, 13 (1973).
25. H. Nogami, T. Nagai and T. Yotsuyanagi, Chem. Pharm. Bull., 17, 499 (1969).
26. K. Sekiguchi, M. Kanke, Y. Tsuda, K. Ishida and Y. Tsuda. Chem. Pharm. Bull., 21, 1592 (1973).
27. W.L. Chiou and S. Niazi, J. Pharm. Sci., 60, 1333 (1971).
28. A.P. Simonelli, S.C. Mehta and W.I. Higuchi, J. Pharm. Sci., 65, 355 (1976).

PHYSICOCHEMICAL PROPERTIES OF INDOMETHACIN AND  
RELATED COMPOUNDS CO-SPRAY DRIED WITH POLYVINYL-  
PYRROLIDONE.

O.I. Corrigan, E.M. Holohan and M.R. Reilly.  
Department of Pharmaceutics, School of Pharmacy,  
Trinity College, 18 Shrewsbury Road, Dublin 4,  
Ireland.

ABSTRACT

The spray drying of indomethacin produced a viscous liquid phase which then solidified to an amorphous glassy solid mass. This amorphous phase was physically unstable and converted on storage to crystalline indomethacin forms II and I. Co-spray drying indomethacin with up to 20% PVP also gave a fused amorphous solid. Apparent solubility and dissolution studies illustrated the higher energy of indomethacin in these systems. The presence of PVP in the solid retarded conversion of indomethacin to a crystalline phase, the effect increasing with increasing PVP content. Scanning electron microscopy revealed the growth, with time, of needle-like whiskers on the surface of the amorphous products. Co-spray drying indo-



methacin with more than 20% PVP resulted firstly in products composed of a fused network of spherical particles, then partially coalesced spheres and ultimately, above 25% PVP, in individual agglomerated microspherical particles. The spray drying of either naproxen, ketoprofen or ibuprofen did not result in the formation of an amorphous glassy solid. Co-spray drying with PVP led to reduced crystallinity; the size of the melting endotherm decreased with increasing PVP content and became absent at 50% PVP. As the PVP percentage increased a microspherical product also developed, but at PVP levels greater than that observed for indomethacin.

#### INTRODUCTION

Spray drying is increasingly used in the production of pharmaceutical products and this process can alter biopharmaceutically relevant drug properties<sup>1</sup>. Previously we investigated the physicochemical properties of a number of spray dried thiazide diuretics<sup>2,3</sup>. These compounds had melting points in the range 200 - 340°C and, on spray drying from ethanolic solution, gave microspherical amorphous glassy particles of varying physical stability with higher activities than the normal crystalline drug forms<sup>3</sup>. Both these pro-

perties, namely small particle size and higher activity, offer potential biopharmaceutical advantage. We have extended these investigations to other drug groups including a number of non-steroidal anti-inflammatory agents of low melting point (M.P.) i.e. indomethacin (158-162°C) naproxen (156°C), ketoprofen (94.5°C) and ibuprofen (75-77.5°C). Indomethacin is known to exist in a number of polymorphic states and also in an amorphous form<sup>4</sup> which has a significantly higher solubility than the crystalline phases<sup>5</sup>. The amorphous form is, however, unstable, being converted to crystalline form I and II<sup>5</sup>. The dissolution kinetics of indomethacin-polyvinylpyrrolidone coprecipitates have also been investigated<sup>6,7</sup>. Recently the stabilization of amorphous indomethacin formed in indomethacin-polyvinylpolypyrrolidone (1:3) systems was reported<sup>8</sup>. Solid dispersion systems of indomethacin and polyethylene glycol (PEG) have also been examined<sup>9,10</sup> and drug dissolution rate related to its degree of crystallinity in the sample<sup>10</sup>. Solid dispersions of ketoprofen have also been investigated and the freeze dried ketoprofen:PVP (1:2) system reported to contain amorphous drug<sup>11</sup>. In contrast, ketoprofen:urea solid dispersions had the characteristics of a simple eutectic mixture<sup>12</sup>. In this communication, the physicochemical

properties of indomethacin and a number of related anti-inflammatory agents, each spray dried both in the presence and absence of PVP, are reported.

### MATERIALS AND METHODS

#### Preparation of Spray Dried Samples

Materials to be spray dried were dissolved in alcoholic solvent. The solution was dried using a Buchi Minispray 190 spray drier, as previously described<sup>2</sup>.

Indomethacin, naproxen, ketoprofen and ibuprofen of B.P. grade were used without further purification. PVP (plasdone c-15) of approximate molecular weight 10,000 was used.

#### X-ray Diffraction and Infra-red Analysis

X-ray diffraction patterns were obtained on powder samples using nickel filtered copper radiation. Both the K Br disc and Nujol mull methods were used for infra-red analysis.

#### Differential Scanning Calorimetry (DSC)

Samples, 2 - 4 mg, were examined using a Perkin Elmer Model DSC 1B instrument at a scanning speed of  $16^{\circ} \text{ min}^{-1}$ .

#### Microscopy

Photomicrographs of spray dried particles were obtained using a Jeol J S M - T200 Scanning Electron Microscope (SEM) and a Hitachi S-520 SEM.

### Solubility and Dissolution Rate

Solubilities and apparent solubilities in phosphate buffer pH 6.6 were determined by the modified method of Shefter and Higuchi<sup>13</sup> as previously described<sup>2</sup>. Apparent solubilities of metastable systems were also determined in media containing 1% PVP in order to inhibit transformation of the metastable phase.

Dissolution profiles were determined from compressed discs of drug mounted in paraffin wax as previously described<sup>14</sup>. Drug in solution was assayed by UV spectroscopy.

### Thin Layer Chromatography

Ethanollic solutions of indomethacin spray dried systems were each spotted on 0.3 mm silica gel 60 GF 254 plates. Plates were developed with methanol-strong ammonia solution 100:1.5, air dried and visualized under UV light.

## RESULTS AND DISCUSSION

### Indomethacin

On spray drying indomethacin from ethanolic solution a highly viscous phase formed, mainly in the cyclone separator above the collecting vessel, which then solidified to give a glassy amorphous form of drug. Spray dried systems containing

indomethacin were slightly yellow in colour. However, only one spot was detected by TLC, the spray dried material having the same  $R_f$  value as pure indomethacin. Both samples were equivalent on U.V. assay indicating insignificant decomposition on spray drying. X-ray diffraction (Fig. 1) and DSC (Fig. 2) scans of indomethacin confirmed the amorphous nature of the spray dried product. Thus it appears that the liquid droplets of drug formed during the spray drying process have insufficient time to solidify and coalesced on contact in the cyclone separator. The product, although amorphous, was in sharp contrast to the microspherical amorphous particles which were recovered from the collecting vessel on spray drying the high melting point thiazide diuretics<sup>3</sup>.

Amorphous indomethacin developed crystallinity within a week. DSC profiles of freshly spray dried indomethacin (Fig. 2) had three peaks, an exotherm, corresponding to reversion of the amorphous phase to form II, a first endotherm suggesting conversion of form II to form I and a second endotherm indicating melting of form I. On storage the size of the exotherm and of the form II endotherm decreased. X-ray diffraction scans of a sample in transition showed traces of peaks of both form

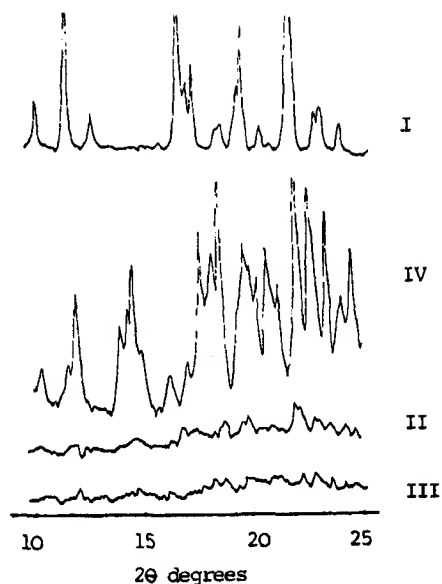


FIGURE 1

X-ray diffractograms of indomethacin systems. I, crystalline drug (form I); II, spray dried drug; III, drug spray dried with 10% PVP and IV, drug spray dried with 5% PVP and stored for two months.

II and form I. Therefore it is not clear whether conversion of the amorphous phase to form I occurs directly or via form II. DSC thermograms obtained on spray dried samples after one year's storage at room temperature still revealed traces of form II.

#### Indomethacin:PVP Spray Dried Systems

Samples prepared by co-spray drying indomethacin and PVP from ethanolic solutions were also amorphous. The high activity of these amorphous systems was confirmed by dynamic solubility and intrinsic dissolution rate experiments. The sol-

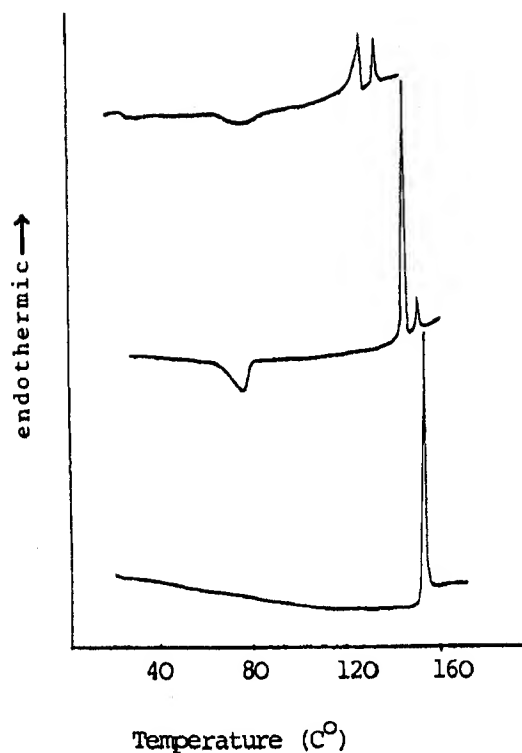


FIGURE 2

DSC scans of I, indomethacin (form I); II, spray dried indomethacin and III, indomethacin spray dried with 5% PVP (freshly prepared).

ubility profile for the amorphous system containing 1% PVP is compared to that of crystalline (form I) in Fig. 3. The amorphous system containing 1% PVP had a peak indomethacin solubility approximately five times that of form I. The inclusion of PVP in the solubility medium to retard crystallization, increased the solubility of both crystalline and amorphous drug indicating soluble complex formation between indomethacin and PVP in solution. Co-spray

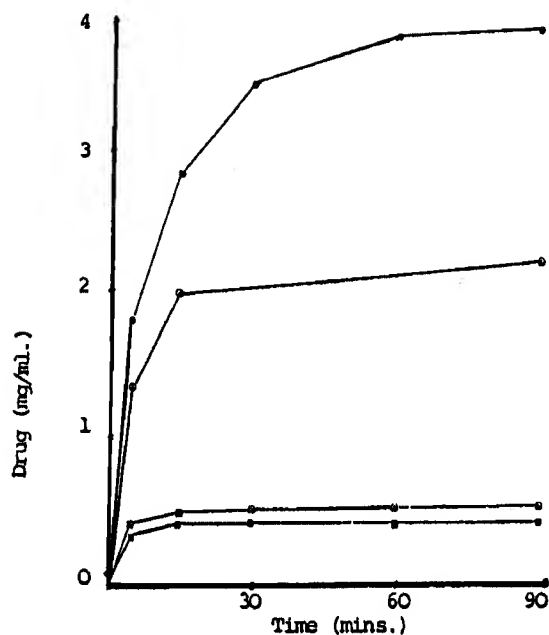


FIGURE 3

Solubility profiles for indomethacin systems. Key: ■ indomethacin (non spray dried), ○ spray dried sample (indomethacin:PVP 99:1), □ indomethacin (non spray dried) in dissolution medium containing 1% PVP and ● spray dried sample (Indomethacin:PVP 99:1) in dissolution medium containing 1% PVP.

drying indomethacin with higher percentages of PVP gave products with even higher apparent peak solubility. However these systems were physically less stable, rapidly crystallizing from solution even in media containing 1% PVP.

Fig. 4 shows the dissolution profiles of an indomethacin:PVP (10% PVP) co-spray dried system, the corresponding crystalline drug:PVP physical mixture and pure indomethacin (form I) obtained using constant surface area discs. The release rate from



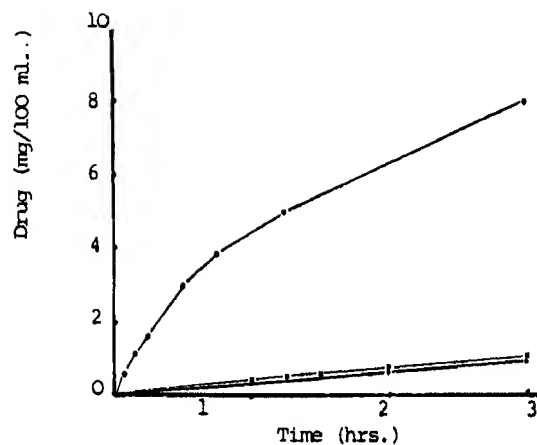


FIGURE 4

Dissolution profiles of constant surface area discs. Key ● indomethacin spray dried with 10% PVP, ▲ physical mixture containing 10% PVP and ■ crystalline indomethacin.

the amorphous phase was over twenty times that observed for crystalline form I.

The physical stability of indomethacin as an amorphous phase improved when the drug was co-spray dried with PVP, the effect increasing as the proportion of PVP in the solid increased. As little as 1% PVP retarded the conversion to crystalline indomethacin. Some conversion to the crystalline phase was evident after twelve days storage in the case of the system containing 1% PVP. Furthermore, when crystallization occurred in PVP containing systems, form I was not the dominant phase as can be seen from the X-ray diffraction pattern for a 2 month-old system spray dried to contain indomethacin with 5%

PVP (Fig. 1). Scanning electron micrographs of these systems revealed the growth of whisker-like, needle-shaped projections on the solid amorphous glassy phase surface (Fig. 5). These whiskers, which appeared to develop less rapidly as the proportion of PVP co-spray dried with the drug increased, became more numerous with time. The growth of needle-shaped crystals in indomethacin systems has been reported to be commensurate with form II indomethacin<sup>4,9</sup>. Surprisingly, even when substantial surface whisker growth was evident from scanning electron microscopy in the 10% PVP system, the sample appeared amorphous by the X-ray diffraction method. While the development of hairlike or whisker-like growths has long been known in inorganic systems<sup>15</sup>, it appears to be less common in organic systems. In the pharmaceutical area, whisker growth on the surface of ethenzamide and caffeine anhydride tablets has been reported<sup>16</sup>. Technological interest in whiskers has centered on their reported ultra high strength and potential use in high strength, light weight whisker reinforced composite materials. Whether they have direct pharmaceutical applications remains to be explored.

In addition to improving the stability of the amorphous product, co-spray drying with PVP also

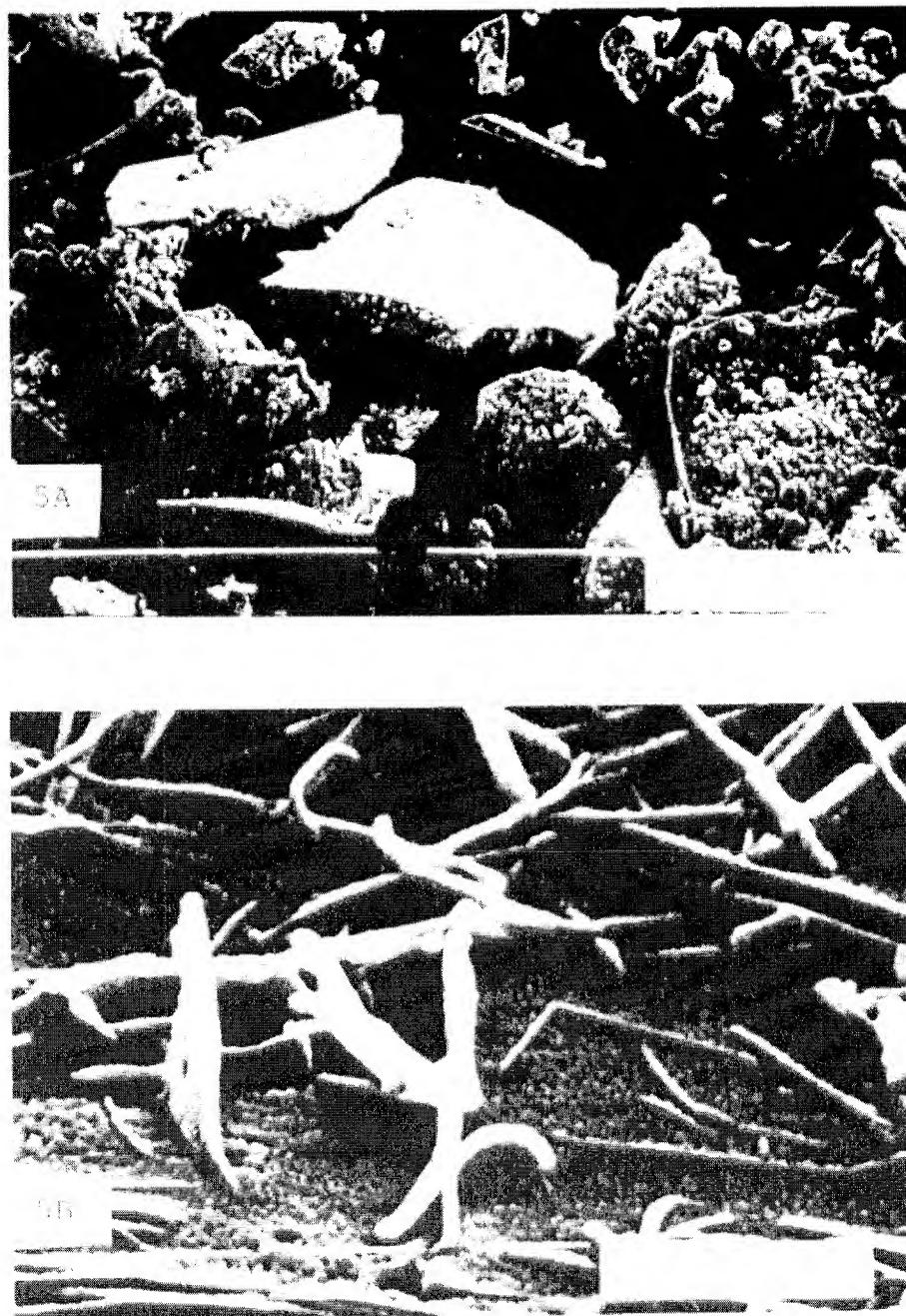


FIGURE 5

Scanning electron micrographs of indomethacin spray dried with 5% PVP. A : bars represents 1000  $\mu\text{m}$ ,  
B : bars represents 1.0  $\mu\text{m}$ .

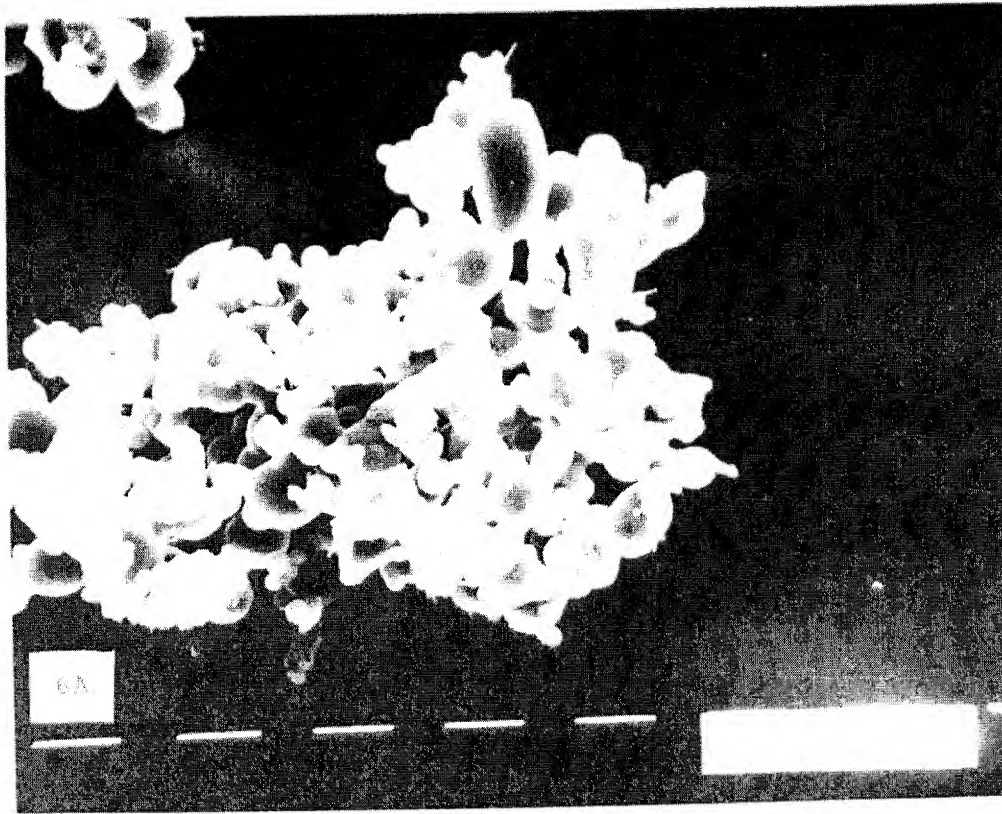


FIGURE 6

Scanning electron micrographs of indomethacin samples spray dried with PVP.

A and B : 20% PVP, bars represent 10  $\mu\text{m}$   
C : 33 $\frac{1}{3}$  % PVP, bars represent 10  $\mu\text{m}$   
D : 33 $\frac{1}{3}$  % PVP, bars represent 1.0  $\mu\text{m}$

dramatically altered the physical properties of the spray dried material. Indomethacin:PVP spray-dried systems containing up to 20% PVP were physically similar to pure spray-dried amorphous indomethacin in that the dried spray droplets coalesced during drying to form an amorphous coating of product in the cyclone separator. When the

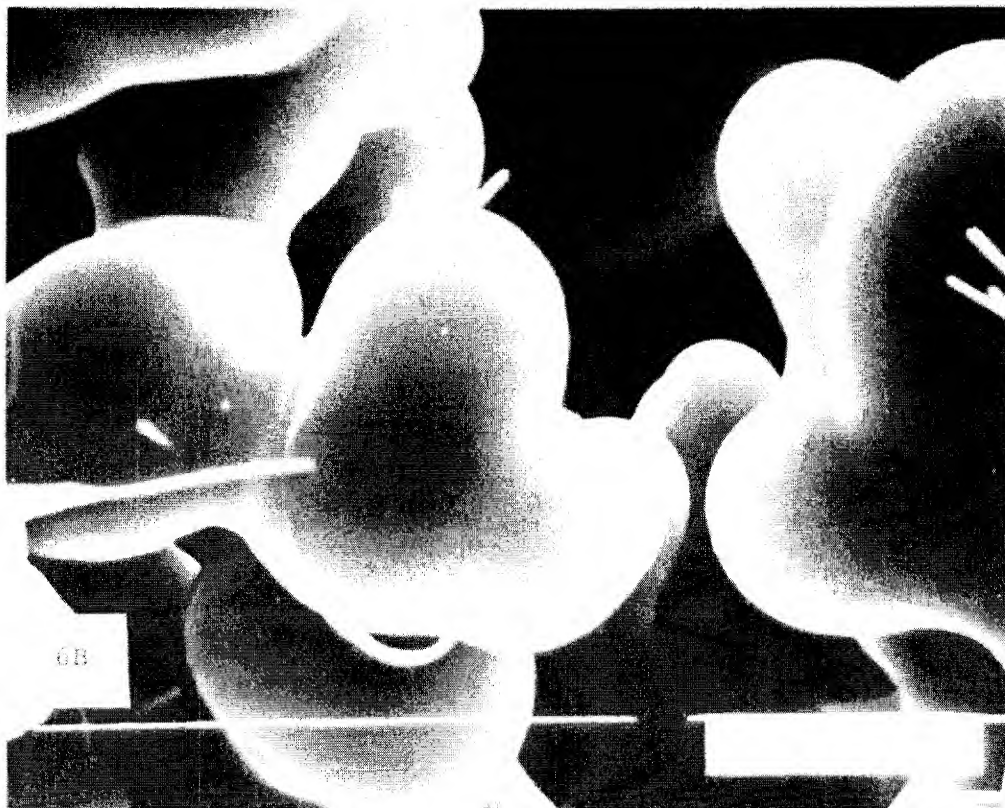


Figure 6 (Continued)

proportion of PVP co-spray dried with indomethacin was further increased, i.e. in the range 20-35%, a change in the properties of the resultant solid occurred. At these higher PVP percentages, a powder formed in the collecting vessel which proved under SEM to be agglomerated microspherical amorphous particles (Fig. 6). At intermediate PVP percentages, the transition from an amorphous slab to a more open network of partially coalesced spheres was

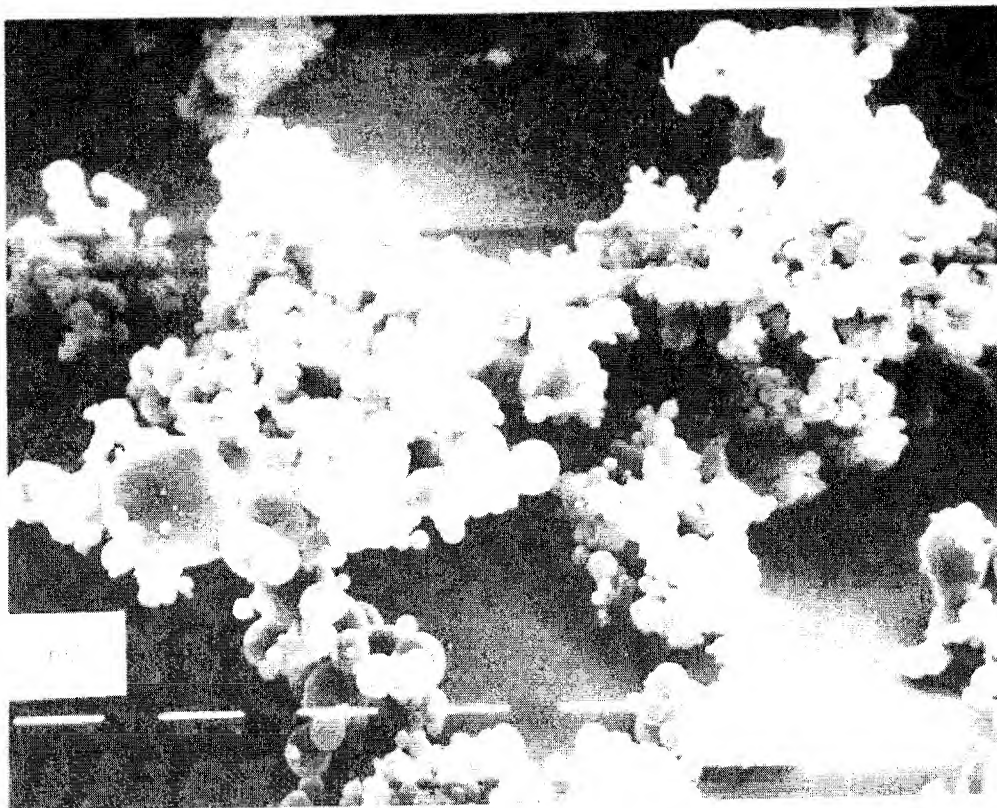


Figure 6 (Continued)

evident. The growth of needle-like whiskers was not evident in systems containing 25% or more of PVP.

#### Naproxen

A crystalline product was formed on spray-drying naproxen in ethanolic solution. Crystallinity was confirmed by both X-ray diffraction and D.S.C. methods. Co-spray drying this drug with increasing amounts of PVP resulted in a decrease in crystallinity. No endothermic peak was evident in the thermogram at 40% PVP. X-ray diffraction peak intensities also decreased with increasing PVP content, only a trace of the major peak being detectable at 40% PVP. However scanning electron microscopy of naproxen:PVP spray dried samples revealed the presence of surface crystals of drug even in systems containing up to 60% PVP, the formation of true amorphous microspherical particles only occurring in systems containing as much as 70% PVP (Fig. 7).

Although naproxen has a similar melting point to indomethacin, it has a much smaller molecular weight. We have previously observed that lower molecular weight compounds less readily form an amorphous phase.<sup>3</sup>

#### Ketoprofen and Ibuprofen

The products produced on spray drying either ketoprofen or ibuprofen were highly viscous transparent liquids. In contrast to indomethacin and





FIGURE 7

Scanning electron micrographs of naproxen spray dried with PVP.

- A : 40% PVP magnifications x 130 and x 650  
B : 75% PVP magnifications x 1,040 and x 5,200



naproxen both ketoprofen and ibuprofen have melting points below 100°C. Co-spray drying ketoprofen or ibuprofen with sufficient PVP gave amorphous solid products. An agglomerated powder was formed at 50% PVP with ketoprofen, while ibuprofen systems of similar composition were still fluid. When co-spray dried with 75% PVP both drugs gave products which were microspherical on SEM examination.

#### ACKNOWLEDGEMENTS

This work was supported by a National Board for Science and Technology Grant (Higher Education - Industrial Cooperation Scheme) number 29/80 and Elan Corporation Limited, Athlone, Ireland.

The authors also wish to thank Dr. C.J. Stillman, Geology Department Trinity College Dublin, for X-ray diffraction facilities and Mr. D. Simpson, Micro-electronics and Electrical Engineering Department and Mr. C. Reid, Electron Microscopy Unit, Trinity College Dublin for the Scanning Electron Micrographs.

#### REFERENCES

1. E. Nurnberg, Acta Pharm. Techn., 26, 39 (1980).
2. O.I. Corrigan, K. Sabra and E.M. Holohan, Drug Devel. Ind. Pharm. 9, 1 (1983).
3. O.I. Corrigan, E.M. Holohan and K. Sabra, Int. J. Pharm. (in press), 18, 195 (1984).

4. L. Borka, *Acta Pharm. Suecica*, 11, 295 (1974)
5. H. Imaizumi, N. Nambu and T. Nagai, *Chem. Pharm. Bull.* 28, 2565 (1980)
6. K. Takayama, N. Nambu and T. Nagai, *Chem. Pharm. Bull.* 28, 3309 (1980)
7. K. Takayama, N. Nambu and T. Nagai, *Chem. Pharm. Bull.* 29, 2718 (1981)
8. H. Imaizumi, N. Nambu and T. Nagai, *Chem. Pharm. Bull.* 31, 2510 (1983)
9. J. L. Ford and M. H. Rubinstein, *Pharm. Acta Helv.* 53, 93 (1978)
10. D. J. Allen and K. C. Kwan, *J. Pharm. Sci.* 58, 1190 (1969)
11. K. Takayama, N. Nambu and T. Nagai, *Chem. Pharm. Bull.* 30, 3013 (1982)
12. J. A. Rogers and A. J. Anderson, *Pharm. Acta Helv.* 57, 276 (1982)
13. E. Shefter and T. Higuchi, *J. Pharm. Sci.*, 52 781 (1963)
14. O. I. Corrigan and R. F. Timoney, *J. Pharm. Pharmac.* 27, 759 (1975)
15. A. P. Levitt in "Whisker Technology" Wiley-Interscience (1970)
16. H. Yuasa, K. Miyata, T. Ando, Y. Kanaya, K. Asahina and H. Murryama. *Yakuzai Gaku* 41, 155 (1981).



## Predicting the physical state of spray dried composites: salbutamol sulphate/lactose and salbutamol sulphate/polyethylene glycol co-spray dried systems

Deirdre O. Corrigan, Owen I. Corrigan, Anne Marie Healy\*

*Department of Pharmaceutics and Pharmaceutical Technology, School of Pharmacy, Trinity College, Dublin 2, Ireland*

Received 12 August 2003; received in revised form 16 December 2003; accepted 6 January 2004

### Abstract

The effect of spray drying salbutamol sulphate, salbutamol sulphate/lactose and salbutamol sulphate/polyethylene glycol (PEG) solutions was investigated. Co-spray drying salbutamol sulphate with lactose, which is amorphous when spray dried alone, resulted in amorphous composites. Co-spray drying salbutamol sulphate with PEG 4000 and PEG 20,000, which do not form amorphous systems when spray dried alone, resulted in systems of varying crystallinity, the crystallinity depending on the weight ratio of polymer to drug.

Examination of the physical properties of these salbutamol sulphate co-spray dried systems and those of bendroflumethiazide/PEG and lactose/PEG composites suggested that the formation and physical stability of amorphous composites prepared by spray drying is dependant on whether the glass transition temperature,  $T_g$ , of one of the two components is high enough to result in a  $T_g$  of the composite sufficiently high that the Kauzmann temperature of the mix is greater than the temperature of storage. The modified Gordon–Taylor equation proved to be useful in predicting the likelihood that a two-component composite will be amorphous on spray drying. Furthermore, the Gordon–Taylor equation was also useful in predicting the likely physical stability of amorphous two component composites and predicted that even polymers with apparently low  $T_g$ s, such as PEGs, may be stabilised in an amorphous composite by a suitable additive having a sufficiently high  $T_g$ .

© 2004 Elsevier B.V. All rights reserved.

**Keywords:** Spray dried composites; Salbutamol sulphate; Physical stability prediction; Gordon–Taylor equation

### 1. Introduction

Salbutamol is widely used in inhaler products. Dry powder inhaler formulations generally consist of micronised drug and inert coarse carrier particles. The excipients are included to aid flow and dispersibility of drug particles, which may be highly cohesive when micronised (Timsina et al., 1994). Inclusion

of a carrier excipient also overcomes the problem of dose metering if fractions of a milligram of a potent medicament are to be delivered (Ganderton and Jones, 1992). Spray drying is known for its ability to produce fine microspherical powders with good flow properties and therefore should prove a useful method of production for inhalation products, especially for the production of powders for dry powder inhalers. Since co-spray drying for inhalation delivery appears to have advantages, in terms of powder particle size and flowability, as well as uniformity of the mix, the model drug salbutamol sulphate was co-spray dried with

\* Corresponding author. Tel.: +353-1-6081444;  
fax: +353-1-6082783.

E-mail address: [healyam@tcd.ie](mailto:healyam@tcd.ie) (A.M. Healy).

various proportions of lactose and polyethylene glycols (PEGs) and their solid state properties evaluated.

In this paper, we also examine the predicted glass transition temperatures and Kauzmann temperatures of salbutamol sulphate co-spray dried systems together with those of previously co-spray dried systems such as lactose/PEG (Corrigan et al., 2002) and bendroflumethiazide/PEG systems (Corrigan et al., 2003). Compatible blends of amorphous materials exhibit a single glass transition ( $T_g$ ) intermediate between the  $T_g$  values of the individual components (Hancock and Zografi, 1994). The higher the  $T_g$  is relative to the actual storage temperature the more stable the system will be. The Kauzmann temperature is generally accepted as the temperature below which translational and rotational motions cease on pharmaceutically relevant time scales (Hancock et al., 1995). Metastable amorphous materials are expected to be physically stable when stored at a temperature less than or equal to their Kauzmann temperature (Hancock et al., 1995; Zhou et al., 2002).

## 2. Experimental

### 2.1. Materials

Salbutamol sulphate was kindly provided by IVAX Pharmaceuticals, Ireland, PEG 4000 was purchased from Riedel de Haën (Germany) and PEG 20,000 was purchased from Fluka. Physical mixes were prepared using sub 125  $\mu\text{m}$  mesh sieved powders mixed in a Turbula Mixer<sup>TM</sup> for 5 min (at 42 rpm).

All spray dried systems were analysed by DSC and XRD within 1 h of production.

### 2.2. Spray drying methodology

Salbutamol sulphate was spray dried as a 10% w/v aqueous solution and as a 0.6% w/v solution from ethanolic solvent consisting of 75% ethanol and 25% water. A Büchi 190 spray drier was used. When spray drying the aqueous solution, an inlet air temperature of 150–152 °C, an outlet temperature of 75–78 °C, pump setting 7, and an airflow rate of 650 l/h were used. When spray drying the ethanolic solution an inlet air temperature of 100–102 °C, an outlet temperature of 60–64 °C, a pump rate setting of 6%, and an airflow rate of 500 l/h were used.

Salbutamol sulphate/lactose systems, consisting of 5, 20 and 40% lactose by weight of total solids, were spray dried as 10% w/v aqueous solutions using a Büchi 191 spray drier with an inlet air temperature of 150 °C, an outlet air temperature of 103–105 °C, a pump rate setting of 10% and airflow rate of 600 l/h. The 20% lactose system was also spray dried at a feed concentration of 2.5% w/v from an aqueous solution under the same conditions except that the outlet temperature range was 98–103 °C.

Salbutamol sulphate/PEG 4000 systems consisting of 5, 20 and 40% PEG 4000 by weight of total solids were spray dried as 2.5% w/v aqueous solutions using a Büchi 191 with an inlet air temperature of 150 °C, outlet temperatures of 91–97, 92–97 and 95–98 °C for the 5, 20 and 40% PEG 4000 systems, respectively, a pump rate setting of 18% and airflow rate of 600 l/h.

Salbutamol sulphate/PEG 20,000 systems consisting of 5, 20 and 40% PEG 20,000 by weight of total solids were spray dried as 2.5% w/v aqueous solutions using a Büchi 191 and the same conditions as for the PEG 4000 systems, except that the outlet temperatures were 100–105, 90 and 96–100 °C, for the 5, 20 and 40% PEG 4000 systems, respectively.

### 2.3. Assessment of physicochemical properties

X-ray powder diffraction measurements (XRD) were made on samples using a Siemens D500 Diffractometer as previously described (Corrigan et al., 2002).

Differential scanning calorimetry (DSC) was performed using a Mettler Toledo DSC 821<sup>e</sup> as previously described (Corrigan et al., 2002).

Scanning electron microscopy (SEM) was performed using a Hitachi S-3500N variable pressure scanning electron microscope.

Energy Dispersive X-Ray Analysis (EDXA) was carried out using Princeton Gamma Tech Imix-PTS EDX analysis on the Hitachi S-3500N variable pressure SEM with a 10 mm<sup>2</sup> UTW detector. For qualitative EDXA, powder samples were utilised and an area mapped for the presence of the atom being analysed.

HPLC analysis of salbutamol sulphate was performed using a variation of the USP Pharmacopeia (USP Pharmacopeia, 2000) method for HPLC analysis of salbutamol sulphate, with sodium-1-heptanesulfonic acid used in the preparation of the mobile

phase instead of sodium-1-hexane-sulfonic acid. A C18 column (Techopak 10 C18, Labquip) attached to a Shimadzu LC-10 AT VP liquid chromatograph with a Shimadzu SCL-10A system controller, a Shimadzu SPD-10A VP UV-Vis detector, a Shimadzu DGU-14 degasser and a SIL-10AD VP autoinjector was used and the system was operated at a flow rate of 1 ml/min. Samples were analysed using Shimadzu Class VP software (version 6.10).

True density measurements were performed by helium pycnometry using a calibrated AccuPyc 1330 instrument (Micromeritics, USA). Prior to analysis, the samples were dried overnight to a constant weight in a vacuum oven at 50 °C with a vacuum pressure of 600 mbar. The mass of each sample was accurately determined using a MT5 microbalance (Mettler Toledo, Switzerland). Each sample was analysed in duplicate.

### 3. Results and discussion

#### 3.1. Salbutamol sulphate

Salbutamol sulphate spray dried from water resulted in an amorphous product evidenced by the halo shown by XRD. The production of amorphous salbutamol sulphate on spray drying from aqueous solution was previously reported by Chawla et al. (1994). Spray drying of salbutamol sulphate from ethanolic solution (75%) also yielded a similar amorphous product. The starting material showed an endothermic peak by DSC at a temperature at approximately 200 °C, consistent with the findings of Ward and Schultz (1995) and recently ascribed to decomposition (Larhrib et al., 2003).

The lack of visible exotherms, together with the lower and broader melting endotherms, obtained by DSC of spray dried salbutamol sulphate, is consistent with the material remaining amorphous on heating. HPLC indicated that both spray dried salbutamol sulphates were not altered chemically by the process. EDXA detected sulphur atoms in the spray dried material consistent with the spray dried material remaining as the sulphate salt form. Chawla et al. (1994) spray dried salbutamol sulphate from aqueous solution and compared the infrared spectra to that of their starting material. They also concluded that spray drying did not appear to alter salbutamol sulphate chemically.

SEM micrographs of the spray dried material showed small spherical particles with diameters ranging from approximately 1 to 7 µm and approximately 1 to 3 µm for particles produced from the aqueous and ethanolic solvents, respectively. The surfaces of the particles in both cases were slightly dimpled.

#### 3.2. Salbutamol sulphate/lactose systems

The salbutamol sulphate/lactose 5, 20 and 40% systems were all amorphous, as shown by XRD analysis (Fig. 1). The 20% systems showed similar XRD and DSC scans regardless of the feed concentration at which they were spray dried. The XRD scans of the various spray dried systems show diffuse halos. In contrast a physical mix of salbutamol sulphate/lactose 20% showed peaks attributable to both crystalline components (Fig. 1).

The DSC scans of spray dried salbutamol sulphate/lactose composites and a DSC scan of a physical mix of salbutamol sulphate/lactose 20% is shown in Fig. 2. The DSC scans of the spray dried systems did not show exothermic events indicative of recrystallisation of amorphous material. The spray dried systems did show degradation of salbutamol sulphate on heating, which was not evident in the physical mixes. The DSC scans of the spray dried salbutamol sulphate/lactose systems appeared very similar to the scans of salbutamol sulphate spray dried alone. The spray dried salbutamol sulphate/lactose systems showed broad endotherms prior to 100 °C consistent with loss of absorbed moisture. Two very small endotherms at approximately 120 and 140 °C and a broad melting peak starting at approximately 165 °C, with jagged peaks indicating degradation, were also observed. The lactose used in the physical mix was lactose monohydrate, therefore the endotherm visible in the DSC scan of the physical mix at approximately 150 °C is consistent with the dehydration of the monohydrate. The melting endotherm of spray dried lactose alone by DSC has an onset temperature at 217 °C (Corrigan et al., 2002). In the co-spray dried salbutamol sulphate/lactose systems no distinct peak was observed at this temperature. The melting of lactose may have shifted to a lower temperature and be obscured by the salbutamol sulphate related endotherm. In the case of the physical mix of salbutamol sulphate/lactose, the broad endotherm at approximately

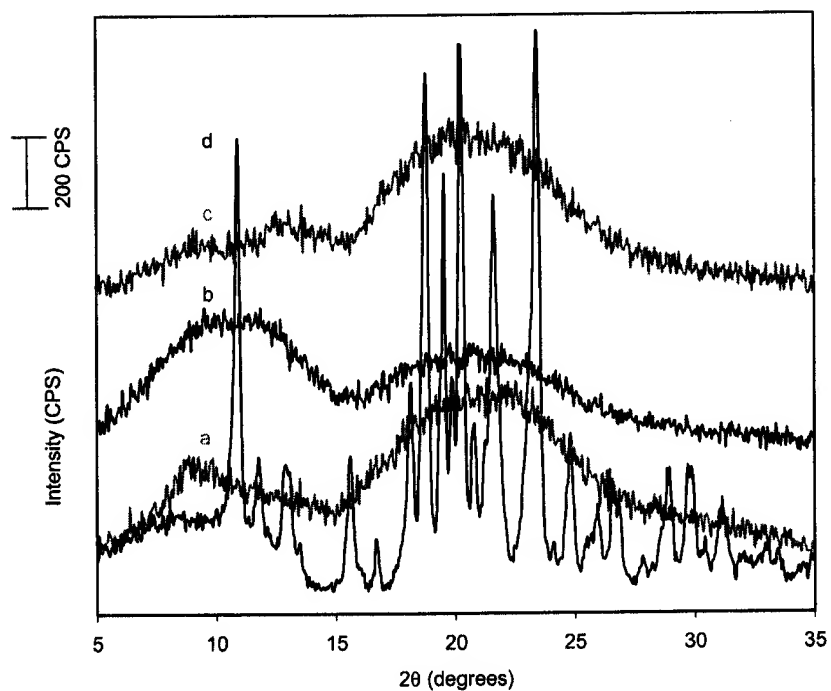


Fig. 1. XRD scans of (a) spray dried salbutamol sulphate/lactose 5%; (b) spray dried salbutamol sulphate/lactose 20%; (c) spray dried salbutamol sulphate/lactose 40%; and (d) physical mix of salbutamol sulphate/lactose 20%.

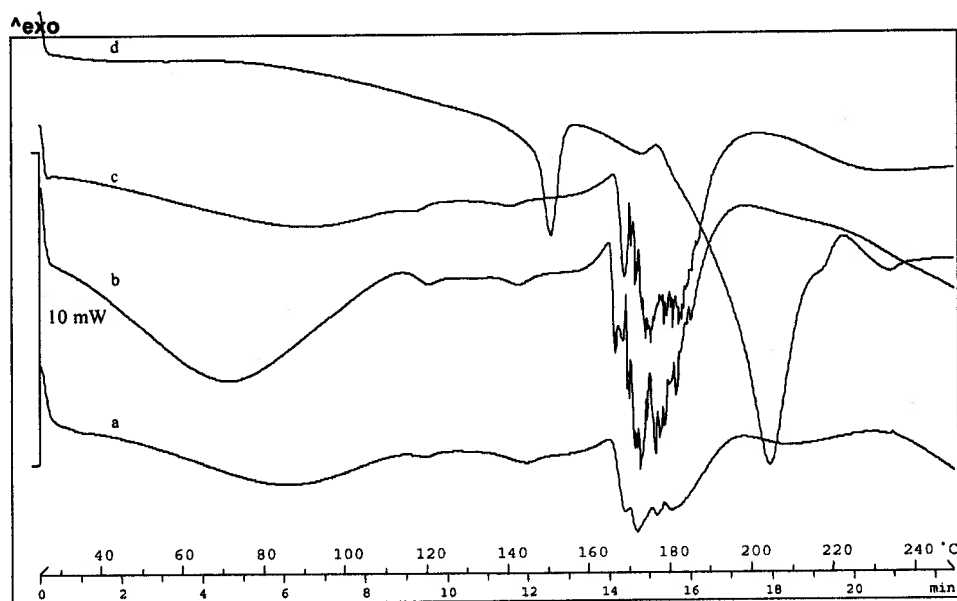


Fig. 2. DSC scans of (a) spray dried salbutamol sulphate/lactose 5%; (b) spray dried salbutamol sulphate/lactose 20%; (c) spray dried salbutamol sulphate/lactose 40%; and (d) physical mix of salbutamol sulphate/lactose monohydrate 20%.

200 °C is likely to be due to the degradation of salbutamol sulphate (Larhrib et al., 2003).

Spray drying salbutamol sulphate/lactose solutions produced a powder, however microscopic examination indicated that the spherical particles produced appeared to absorb moisture and merge together within a matter of seconds. The particles of the salbutamol sulphate/lactose 5% system were approximately 1–15 µm in diameter. Particles of the 20% system spray dried as a 10% w/v solution were approximately 1–20 µm in diameter. Salbutamol sulphate/lactose 20% spray dried at the lower feed concentration of 2.5% w/v resulted in particles with a narrower size distribution, particles being approximately 2–10 µm in diameter. The salbutamol sulphate/lactose 40% system resulted in particles 5–15 µm in diameter. (However, these particles had already started to merge by the time they were gold coated, therefore their true size is expected to be smaller.) Lactose spray dried alone from water (as a 10% w/v solution) produced smooth spherical particles approximately 1–4 µm in diameter. The particle size range for the co-spray dried systems appeared to be broader and larger particles were found than when the individual components were spray dried alone. The inlet–outlet temperature difference was much larger for salbutamol sulphate spray dried from water than for the salbutamol sulphate/lactose co-spray dried systems, however a similar temperature difference, to that

used for the mixed systems, was employed for lactose spray dried alone (Corrigan et al., 2002). A higher airflow was used in spray drying salbutamol sulphate than was used for the salbutamol sulphate/lactose systems. The difference in airflow may be responsible for the particle size differences observed (Masters, 1985).

### 3.3. Salbutamol sulphate/PEG 4000 systems

Fig. 3 shows the XRD scans of spray dried salbutamol sulphate/PEG 4000 composites (containing 5, 20 and 40% PEG 4000 by weight of total solid). No intensity peaks indicative of crystallinity were apparent by XRD for the 5% system. The 20 and 40% PEG 4000 systems did show some peaks indicative of the presence of some crystalline PEG, however these peaks were of low intensity compared to physical mixes, indicating reduction in crystallinity of PEG 4000 during processing.

Previous studies on lactose/PEG 4000 composites, spray dried from water, showed the PEG crystallinity to be reduced on spray drying, the extent being dependent on the concentration of PEG 4000 in the system (Corrigan et al., 2002). PEG was shown to be amorphous when spray dried with lactose at a concentration of 10% PEG, while at other concentrations (5, 20 and 30% PEG 4000), there was evidence of reduced PEG crystallinity.

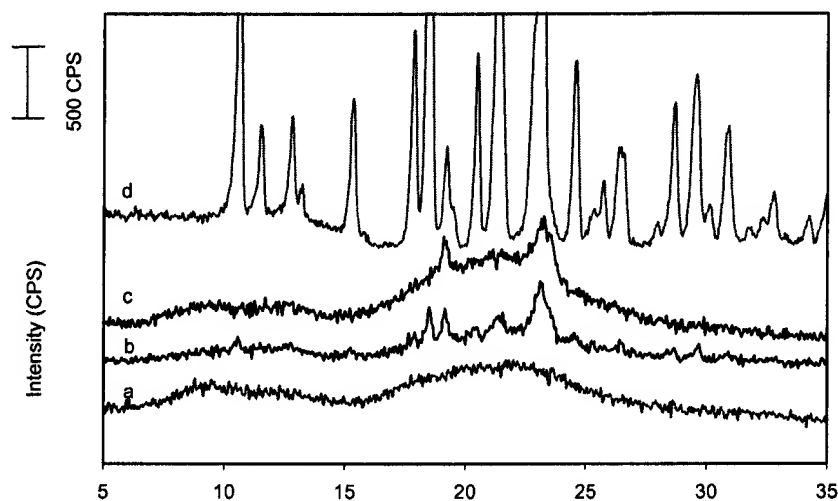


Fig. 3. XRD scans of (a) spray dried salbutamol sulphate/PEG 4000 5%; (b) spray dried salbutamol sulphate/PEG 4000 20%; (c) spray dried salbutamol sulphate/PEG 4000 40%; and (d) physical mix of salbutamol sulphate/PEG 4000 5%.

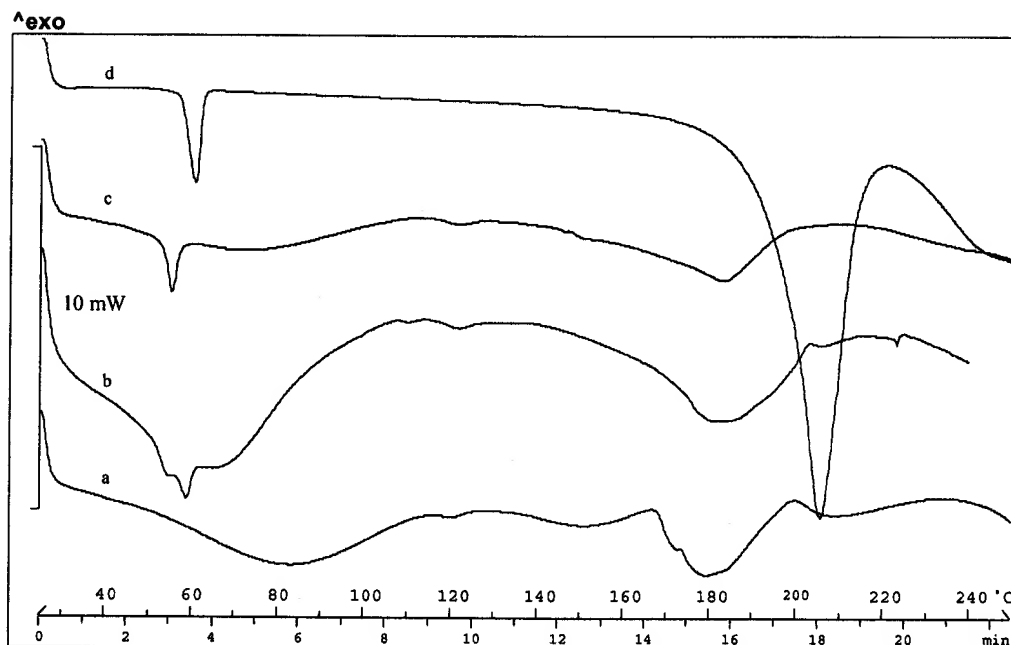


Fig. 4. DSC scans of (a) spray dried salbutamol sulphate/PEG 4000 5%; (b) spray dried salbutamol sulphate/PEG 4000 20%; (c) spray dried salbutamol sulphate/PEG 4000 40%; and (d) physical mix of salbutamol sulphate/PEG 4000 5%.

The salbutamol sulphate/PEG 4000 20% system appeared to contain some crystalline salbutamol sulphate unlike the 40% system, which showed only the two peaks at approximately 19 and 23° 2 $\theta$  attributable to crystalline PEG 4000.

No melting endotherm for PEG 4000 was visible in the DSC scan of the spray dried 5% system, however a melting endotherm for PEG 4000 can be seen for the 5% physical mix (Fig. 4). This indicates that DSC can detect the presence of crystalline PEG 4000 at this level and therefore implies that less than 5% crystalline PEG is present in the spray dried system. The 20% PEG 4000 system showed two melting endotherms for PEG 4000 which could represent melting of some once folded PEG (metastable) as well as melting of the extended chain form of PEG (Chatham, 1985; Kambe, 1980; Corrigan et al., 2002). The 40% PEG 4000 system showed a PEG melting peak, which occurred at a slightly lower temperature than in the equivalent physical mix (possibly due to the presence of the once folded metastable form). The magnitude of the PEG endotherm in the 40% system was less than for the 5% physical mix implying less than 5% crystalline PEG is present. No recrystallisation exotherms

are visible by DSC for any of the spray dried systems and the melting endotherms of salbutamol sulphate are broader and reduced in onset temperature compared to the physical mixes.

SEM micrographs showed spherical salbutamol sulphate/PEG 4000 5% particles with diameters of 4–10  $\mu\text{m}$ . The salbutamol sulphate/PEG 4000 20% system appeared to consist of fused aggregates of spheres (Fig. 5a). Large fused aggregates had diameters of approximately 25–30  $\mu\text{m}$ . Individual spheres were approximately 2–6  $\mu\text{m}$  in diameter. The salbutamol sulphate/PEG 4000 40% SEM micrographs showed spherical structures of approximately 70  $\mu\text{m}$  in diameter, consisting of many tiny particles as well as separate spherical individual particles approximately 1–5  $\mu\text{m}$  in diameter (Fig. 5b).

### 3.4. Salbutamol sulphate/PEG 20,000 systems

Fig. 6 shows the XRD scans of the spray dried salbutamol sulphate/PEG 20,000 systems. The 5 and 20% systems were completely amorphous by XRD with respect to salbutamol sulphate and polymer. The 40% PEG 20,000 system showed peaks indicative of crys-



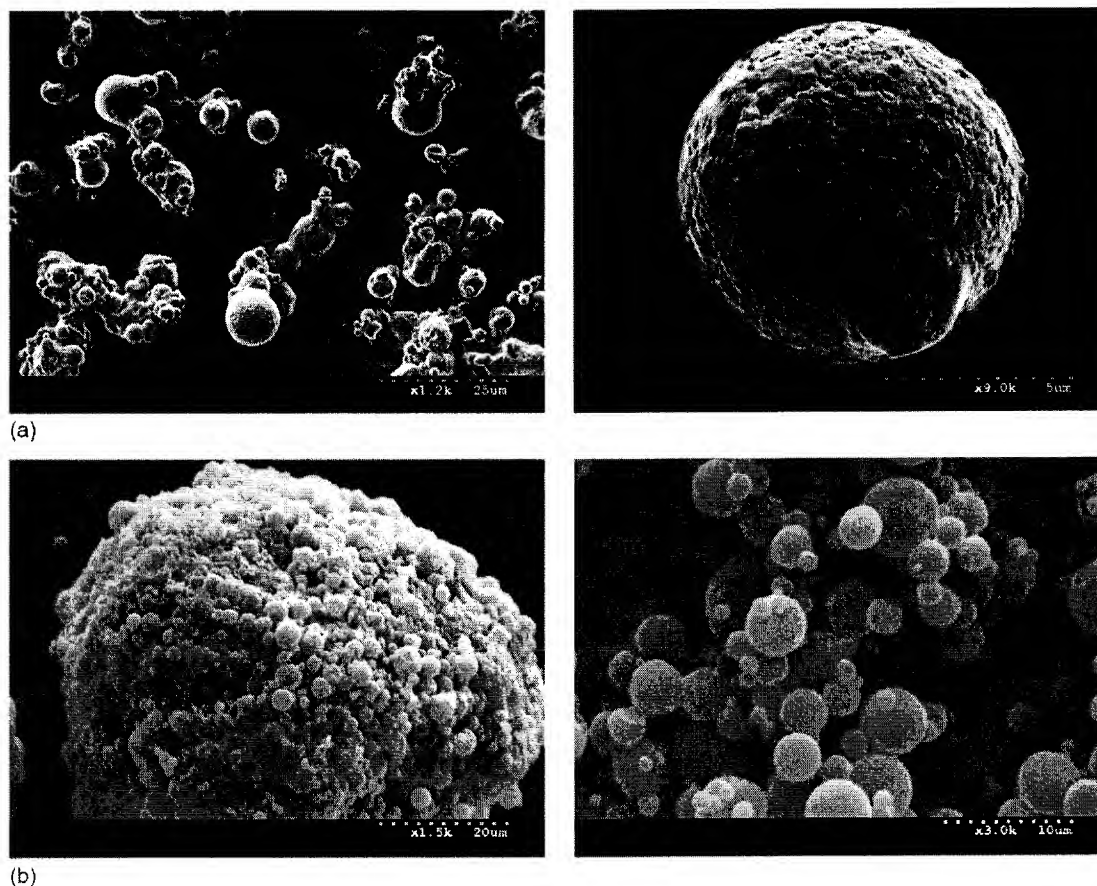


Fig. 5. (a) SEM micrographs of spray dried salbutamol sulphate/PEG 4000 20%. (b) SEM micrographs of spray dried salbutamol sulphate/PEG 4000 40%.

talline PEG 20,000. These peaks were smaller in magnitude than the equivalent physical mix. No peaks were present for crystalline salbutamol sulphate in the 40% system indicating that it is either amorphous or present as a molecular dispersion within the PEG 20,000.

Fig. 7 shows the DSC scans of the various spray dried salbutamol sulphate/PEG 20,000 systems. Neither the 5% nor the 20% system shows an endotherm indicative of melting of crystalline PEG. The 40% PEG 20,000 system does show a melting endotherm in the PEG region but this is much reduced in enthalpy compared to the 40% PEG 20,000 physical mix, being less than half the magnitude of the PEG melting endotherm of the 20% PEG physical mix shown in Fig. 7 (scan d). The spray dried PEG 20,000 20% system showed a distinct exotherm by DSC indicating recrystallisation of amorphous salbutamol sulphate

prior to the salbutamol sulphate endotherm (indicated by the arrow in Fig. 7 (scan b)). This salbutamol sulphate/PEG 20,000 20% system was the only co-spray dried system containing salbutamol sulphate to show a visible recrystallisation exotherm during heating by DSC. The 5 and 40% systems do not show obvious exotherms. Salbutamol sulphate systems spray dried alone did not show recrystallisation exotherms by DSC, nor did other salbutamol sulphate co-spray dried systems. The endotherm for salbutamol sulphate in the 20% PEG 20,000 system is likely due to the presence of some recrystallised salbutamol sulphate as opposed to melting of an amorphous form. This endotherm is quite broad when compared to a physical mix implying that the salbutamol sulphate is perhaps not as crystalline as that in the physical mix. The fact that other salbutamol sulphate spray dried systems

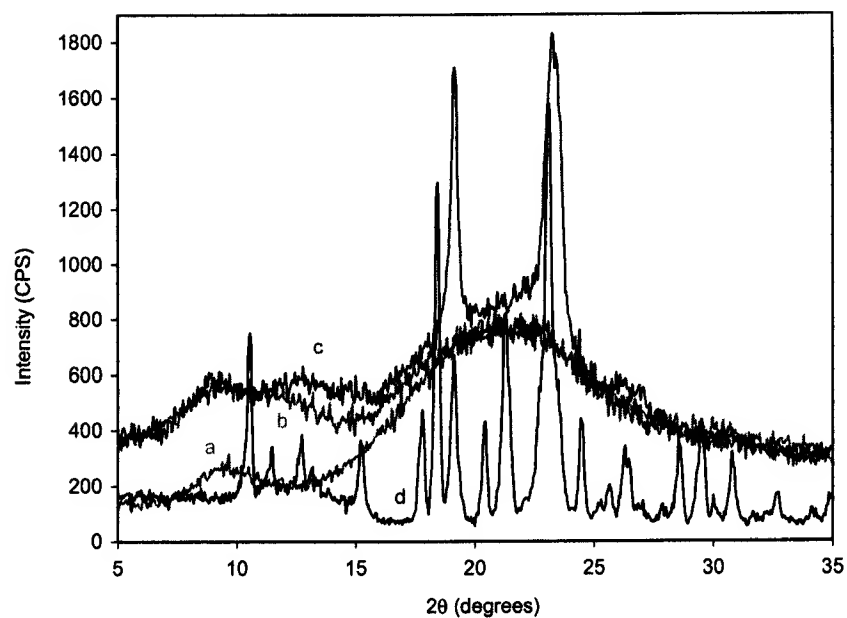


Fig. 6. XRD scans of (a) spray dried salbutamol sulphate/PEG 20,000 5%; (b) spray dried salbutamol sulphate/PEG 20,000 20%; (c) spray dried salbutamol sulphate/PEG 20,000 40%; and (d) physical mix of salbutamol sulphate/PEG 20,000 20%.

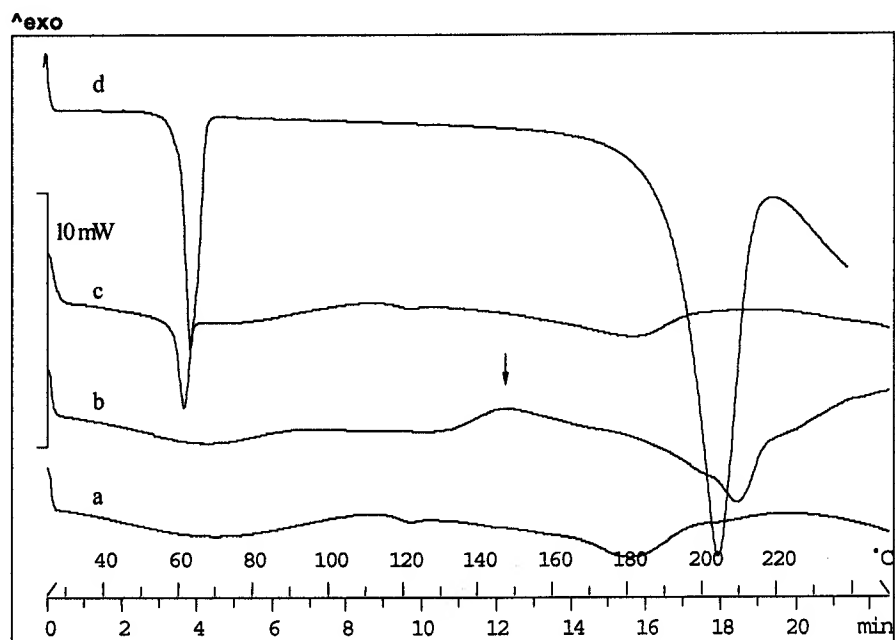


Fig. 7. DSC scans of (a) spray dried salbutamol sulphate/PEG 20,000 5%; (b) spray dried salbutamol sulphate/PEG 20,000 20%; (c) spray dried salbutamol sulphate/PEG 20,000 40%; and (d) physical mix of salbutamol sulphate/PEG 20,000 20%. The arrow indicates the exothermic peak.

show broad lower temperature endotherms which are not preceded by a clear exothermic event implies that the salbutamol sulphate is present as a glass which does not recrystallise on heating. The 20% PEG 20,000 system, therefore, is consistent with the presence of amorphous salbutamol sulphate rather than a solid solution of salbutamol sulphate in PEG 20,000. Chiou and Niazi (1971) investigated solid dispersions of sulfathiazole and urea prepared by the melt method. XRD analysis of the solid dispersion systems showed no peaks indicative of sulfathiazole indicating that it may be present either as a solid solution or as an amorphous phase. Differential thermal analysis of the solid dispersion showed an exotherm followed by a melting endotherm, the melting endotherm occurring at a lower melting temperature than in equivalent physical mixes. On storage the melting endotherm gradually increased in onset melting temperature and weak diffraction lines attributable to sulfathiazole appeared by XRD. They concluded that sulfathiazole was likely to have been present as an amorphous phase rather than as a molecular dispersion based on the fact that sulfathiazole alone shows a tendency to super-cool to a glassy state and because of the presence of a DSC exotherm, a lower onset melting endotherm and the appearance of peaks by XRD following storage.

SEM micrographs of spray dried salbutamol sulphate/PEG 20,000 systems are shown in Fig. 8. The 5 and 40% PEG 20,000 consisted of smooth spherical particles with numerous indentations. The 20% system showed particles that were spherical but with fibrous surfaces. The 5 and 20% PEG 20,000 particles were approximately 2–8  $\mu\text{m}$  in diameter. The 40% PEG 20,000 system consisted of particles with diameters from approximately 2 to 10  $\mu\text{m}$ .

### 3.5. Glass transition temperatures and physical state and stability of spray dried composite materials

The physical form of the composites, i.e. crystalline or amorphous, obtained on spray drying either salbutamol sulphate, lactose (Corrigan et al., 2002) or bendroflumethiazide (BFMT) (Corrigan et al., 2003) with increasing PEG content is summarised in Table 1. Of the three drugs, bendroflumethiazide has the least tendency to crystallise in the presence of increasing amounts of PEG. When spray dried as a single component lactose, bendroflumethiazide and salbutamol

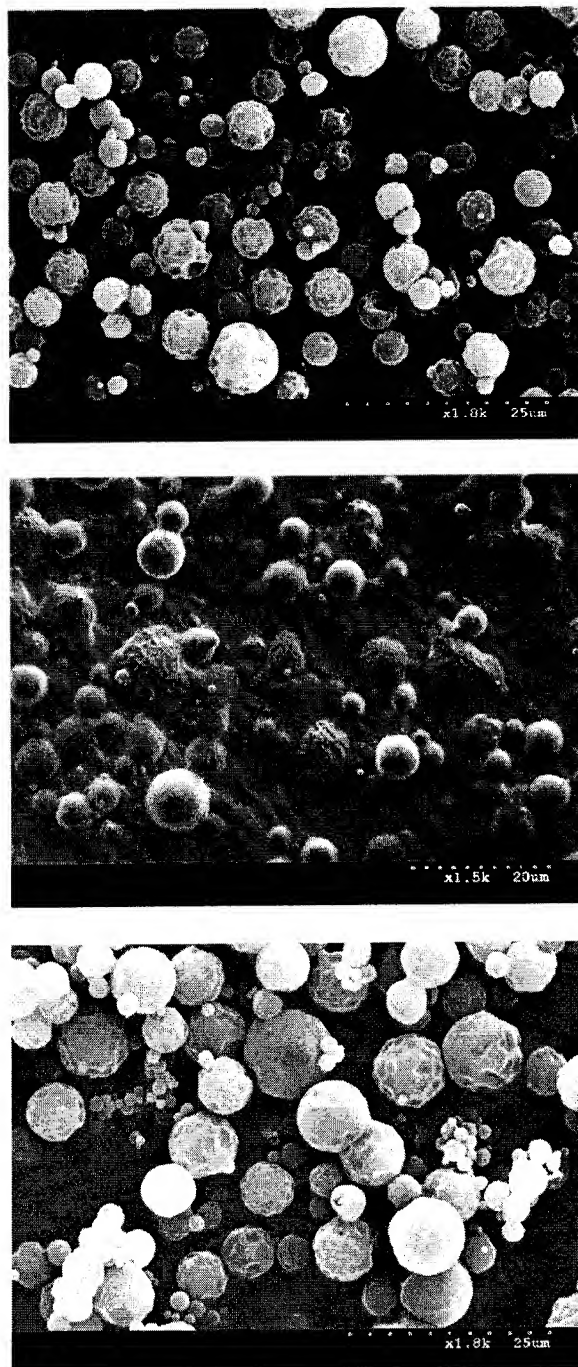


Fig. 8. SEM micrographs of spray dried salbutamol sulphate/PEG 20,000 5% (top), 20% (middle) and 40% (bottom).

Table 1

Crystallinity of PEG 4000 in BFMT/PEG 4000, salbutamol sulphate/PEG 4000 and lactose/PEG 4000 systems

System	PEG 4000 by weight of total solids				
	5%	10%	20%	30%	40%
BFMT/PEG	–	am	am	am	–
Lactose/PEG	am <sup>a</sup>	am	c	c	–
Salbutamol sulphate/PEG	am	–	c	–	c

am: amorphous, c: peaks indicative of crystallinity.

<sup>a</sup> Crystallinity suggested by XRD but not by DSC.

sulphate are amorphous with  $T_g$  above room temperature (Table 2), while PEGs are semicrystalline materials and exhibit a  $T_g$  which depends on the molecular weight of the sample (Craig, 1995). In the molecular weight range of  $10^2$ – $10^7$  the  $T_g$  varies from approximately  $-98$  to  $-17^\circ\text{C}$  depending on molecular weight (Craig, 1995). The very low  $T_g$ s of PEGs indicate that at room temperature, following spray drying, the materials are likely to be crystalline. Previously when Corrigan et al. (1984) spray dried a range of thiazide diuretics they found that the larger molecular weight compounds formed amorphous phases more readily than the lower molecular weight thiazides. Amorphous systems produced from the higher molecular weight thiazides were more physically stable than amorphous systems produced from the lower molecular weight thiazides. The PEGs do not contain large side groups and this might explain why they are less likely to form amorphous systems on spray drying. Bodmeier and Chen (1988) described linear macromolecular polymers without bulky side groups, such as polylactic

acid, as having strong and extensive intermolecular bonding coupled with adhering stiffness of the polymeric chains leading to strong chain interactions. They used these facts to explain the difficult disruption of a liquid filament into individual particles resulting in fibrous spray dried material.

Compatible blends of amorphous materials exhibit a single  $T_g$  that is intermediate between the  $T_g$  values of the individual components (Hancock and Zografi, 1994). The low  $T_g$ s of PEGs indicate that these materials are likely to act as plasticisers and this has been shown previously for systems containing 10, 20 and 30% PEG (with either lactose (Corrigan et al., 2002)) or BFMT (Corrigan et al., 2003). Considering the glass transition behaviour of amorphous solids in terms of polymer free volume theory, the glass transition of a mix of two components ( $T_{g\text{mix}}$ ) can be determined by Eq. (1) (Gordon and Taylor, 1952):

$$T_{g\text{mix}} = \frac{(w_1 T_{g1} + K w_2 T_{g2})}{(w_1 + K w_2)} \quad (1)$$

where  $K = \rho_1(\Delta\alpha_2)/\rho_2(\Delta\alpha_1)$ ,  $\Delta\alpha$  is the thermal expansivity of  $T_g$ ,  $w$  is the weight fraction and  $\rho$  is the true density of the material. Numbers 1 and 2 are indicative of the two different components.

Hancock and Zografi (1994) describe that since  $(\Delta\alpha)T_g$  is approximately constant,  $K$  can be calculated from the densities ( $\rho_1$  and  $\rho_2$ ) of the two components using Eq. (2).

$$K = \frac{\rho_1 T_{g1}}{\rho_2 T_{g2}} \quad (2)$$

$T_{g\text{mix}}$  was calculated for salbutamol sulphate/PEG 4000 systems containing 10, 20 and 30% PEG 4000,

Table 2

The estimated glass transition temperature of a mix of two components systems ( $T_{g\text{mix}}$  ( $^\circ\text{C}$ )) determined from Eq. (1) using the  $K$  value obtained from Eq. (2), and estimated Kauzmann temperatures ( $^\circ\text{C}$ ) calculated as  $T_g - 50\text{K}$ .  $T_g$  of pure drug components are also shown

PEG content in mix (%)	BFMT/PEG 4000		Lactose/PEG 4000		Salbutamol sulphate/ PEG 4000	
	$T_{g\text{mix}}$ ( $^\circ\text{C}$ )	Kauzmann temperature ( $^\circ\text{C}$ )	$T_{g\text{mix}}$ ( $^\circ\text{C}$ )	Kauzmann temperature ( $^\circ\text{C}$ )	$T_{g\text{mix}}$ ( $^\circ\text{C}$ )	Kauzmann temperature ( $^\circ\text{C}$ )
0	120.0	70.0	104.0 <sup>a</sup>	54.0	64.0 <sup>b</sup>	14.0
10	88.3	38.3	76.8	26.8	48.5	-1.5
20	62.7	12.7	54.6	4.6	34.5	-15.5
30	41.8	-8.3	35.8	-14.2	21.9	-28.1

<sup>a</sup> Elamin et al. (1995).

<sup>b</sup> Ward and Schultz (1995).

and also for the BFMT/PEG 4000 and lactose/PEG 4000 reported previously (Corrigan et al., 2002, 2003). True densities were taken as 1.5 g/cm<sup>3</sup> for lactose, 1.18 g/cm<sup>3</sup> for PEG 4000 (Handbook of Pharmaceutical Excipients, 1994) and were measured as 1.27 g/cm<sup>3</sup> for salbutamol sulphate and 1.54 g/cm<sup>3</sup> for BFMT. For PEG 4000 a  $T_g$  of  $-41^\circ\text{C}$  was estimated from  $T_g = 0.7T_m$  (Hancock and Zografi, 1994; Brittain, 1999).

Table 2 shows the  $T_{g\text{mix}}$  data calculated for BFMT/PEG 4000, lactose/PEG 4000 and salbutamol sulphate/PEG 4000 mixed systems. The  $T_{g\text{mix}}$  values for the BFMT/PEG 4000 systems were in good agreement with the values obtained experimentally using modulated DSC (Corrigan et al., 2003). Experimentally obtained values were 83, 69 and  $45^\circ\text{C}$  for the 10, 20 and 30% PEG/BFMT systems, respectively.

The data suggests that amorphous BFMT/PEG systems are more likely to form and be physically more stable at room temperature than lactose/PEG systems, which in turn should be more physically stable than salbutamol sulphate/PEG systems with respect to ease of recrystallisation. This trend was reasonably consistent with the crystallinity of PEG found in these systems as shown in Table 1. The higher the  $T_g$  is above the actual storage temperature, the more stable the system will be. Metastable amorphous materials are expected to be physically stable when stored at a temperature less than or equal to their Kauzmann temperature. The Kauzmann temperature of a material is generally  $\sim 50\text{ K}$  below the  $T_g$  of the material (Hancock et al., 1995; Zhou et al., 2002). Table 2 shows the estimated Kauzmann temperatures of the mixed PEG 4000 systems (based on  $T_g - 50\text{ K}$ ) (Hancock et al., 1995; Zhou et al., 2002).

The Kauzmann temperature estimates in Table 2 indicate that at room temperature the salbutamol sulphate/PEG 4000 systems and the lactose/PEG 4000 20 and 30% systems will not be stable. The lactose/PEG 4000 10% should be stable. Analysis of this system showed it to be the most X-ray amorphous of all the lactose/PEG 4000 systems (Corrigan et al., 2002). The BFMT/PEG 4000 10% should also be stable at room temperature since it has a Kauzmann temperature of  $38^\circ\text{C}$ . The 20 and 30% PEG/BFMT systems have Kauzmann temperatures below room temperature and therefore are likely to be unstable. These systems had

Table 3

The  $T_{g\text{mix}}$  ( $^\circ\text{C}$ ) determined from Eq. (1) using the  $K$  value obtained from Eq. (2), and estimated Kauzmann temperatures ( $^\circ\text{C}$ ) calculated as  $T_g - 50\text{ K}$ , for salbutamol sulphate/lactose systems

System	$T_{g\text{mix}}$ ( $^\circ\text{C}$ )	Kauzmann temperature ( $^\circ\text{C}$ )
Salbutamol sulphate/lactose 5%	65.5	15.5
Salbutamol sulphate/lactose 20%	70.4	20.4
Salbutamol sulphate/lactose 40%	77.4	27.4

not, however, recrystallised by the time they were initially analysed (Corrigan et al., 2003).

The  $T_{g\text{mix}}$  values and the Kauzmann temperatures were also calculated for salbutamol sulphate/lactose mixed systems and are shown in Table 3. The  $T_g$  values used in the calculations were the experimentally derived  $T_g$ s shown in Table 2. The  $T_{g\text{mix}}$  and Kauzmann temperature values increase as the lactose content increases. The salbutamol sulphate/lactose spray dried systems were all amorphous when analysed by XRD which is consistent with the high  $T_{g\text{mix}}$  and Kauzmann temperature values calculated for these systems.

Zhou et al. (2002) produced amorphous forms of several model compounds and determined their Kauzmann temperatures experimentally. Results were generally in agreement with the  $T_g - 50\text{ K}$  values of the compounds. Zhou et al. (2002) described that one of their model amorphous systems, ritonavir, showed excellent physical stability above its Kauzmann temperature. This indicated that although the Kauzmann temperature is a useful parameter, knowledge of the Kauzmann temperature alone is not adequate to understand the physical stability of an amorphous system. Zhou et al. (2002) stated that configurational entropy and molecular mobility values as a function of temperature need to be assessed in addition to  $T_g$  and Kauzmann temperatures. They concluded from their work that compounds with high  $T_g$ s, high configurational entropy barriers, high Kauzmann temperatures and low molecular mobilities are expected to show the greatest stability. The measurement of molecular mobility is beyond the scope of this paper.

#### 4. Conclusions

Co-spray drying salbutamol sulphate with lactose, which is amorphous when spray dried alone, resulted

in amorphous composites. Co-spray drying salbutamol sulphate with PEG 4000 and PEG 20,000, which do not form amorphous systems when spray dried alone, resulted in systems of varying crystallinity, the crystallinity depending on the weight ratio of polymer to drug.

Feed concentration was an important factor in determining particle size of the resultant spray dried powders. Thus, decreasing the feed concentration from 10 to 2.5% w/v resulted in the production of smaller diameter particles with a narrower size distribution.

Depending on the percentage of excipient, differing particle morphologies were found including homogeneous spherical particles, fused particles, large spherical aggregates consisting of many smaller spheres, particles with a smooth surface having indentations and particles with a fibrous surface.

The formation and physical stability of amorphous composites formed by spray drying was found to depend on whether the  $T_g$  of one of the components is high enough to result in a  $T_{g\text{mix}}$  sufficiently high that the Kauzmann temperature of the mix is greater than the temperature of storage. The Gordon–Taylor equation was useful in predicting the likelihood that a two component composite will be amorphous on spray drying. Furthermore, the Gordon–Taylor equation appears to be useful in predicting the likely physical stability of amorphous two component composites and predicted that even polymers with apparently low  $T_g$ s, such as PEGs, may be stabilised in an amorphous composite by a suitable drug/additive with a sufficiently high  $T_g$ .

## Acknowledgements

The authors would like to thank Neal Leddy, Colin Reid and David John of the Electron Microscope Unit, Trinity College, for their help and expertise and also Lidia Tajber for valuable discussion of the work.

## References

- Bodmeier, R., Chen, H., 1988. Preparation of biodegradable polylactide microparticles using a spray drying technique. *J. Pharm. Pharmacol.* 40, 754–757.
- Brittain, H.G., 1999. *Polymorphism in Pharmaceutical Solids*. Marcel Dekker, New York.
- Chatham, S.M., 1985. Characterisation of molten filled hard gelatin capsules. Ph.D. thesis, University of London.
- Chawla, A., Taylor, K.M.G., Newton, J.M., Johnson, M.C.R., 1994. Production of spray dried salbutamol sulphate for use in dry powder aerosol formulation. *Int. J. Pharm.* 108, 233–240.
- Chiou, W.L., Niazi, S., 1971. Phase diagram and dissolution-rate studies on sulfathiazole-urea solid dispersions. *J. Pharm. Sci.* 60, 1333–1337.
- Corrigan, D.O., Healy, A.M., Corrigan, O.I., 2002. The effect of spray drying solutions of polyethylene glycol (PEG) and lactose/PEG on their physicochemical properties. *Int. J. Pharm.* 235, 193–205.
- Corrigan, D.O., Healy, A.M., Corrigan, O.I., 2003. The effect of spray drying solutions of bendroflumethiazide/polyethylene glycol on the physicochemical properties of the resultant materials. *Int. J. Pharm.* 262, 125–137.
- Corrigan, O.I., Holohan, E.M., Sabra, K., 1984. Amorphous forms of thiazide diuretics prepared by spray-drying. *Int. J. Pharm.* 18, 195–200.
- Craig, D.Q.M., 1995. A review of thermal methods used for the analysis of the crystal form, solution thermodynamics and glass transition behaviour of polyethylene glycols. *Thermochim. Acta* 248, 189–203.
- Elamin, A.A., Sebbatu, T., Ahlneck, C., 1995. The use of amorphous model substances to study mechanically activated materials in the solid state. *Int. J. Pharm.* 119, 25–36.
- Ganderton, D., Jones, T., 1992. *Advances in Pharmaceutical Sciences*, vol. 6. Academic Press, London (Chapter 5).
- Gordon, M., Taylor, J.S., 1952. Ideal co-polymers and the second order transitions of synthetic rubbers. 1. Non-crystalline copolymers. *J. Appl. Chem.* 2, 493–500.
- Hancock, B.C., Zografi, G., 1994. The relationship between the glass transition temperature and the water content of amorphous pharmaceutical solids. *Pharm. Res.* 11, 471–477.
- Hancock, B.C., Shamblin, S.L., Zografi, G., 1995. Molecular mobility of amorphous pharmaceutical solids below their glass transition temperatures. *Pharm. Res.* 12, 799–806.
- Handbook of Pharmaceutical Excipients, 1994. In: Wade, A., Weller, P.J. (Eds.), 2nd ed. Pharmaceutical Press, London.
- Kambe, Y., 1980. Thermal behaviour of poly(ethylene oxide) as revealed by differential scanning calorimetry. *Polymer* 21, 352–355.
- Larhrib, H., Martin, G.P., Marriott, C., Prime, D., 2003. The influence of carrier and drug morphology on drug delivery from dry powder formulations. *Int. J. Pharm.* 257, 283–296.
- Masters, K., 1985. *Spray Drying Handbook*, 4th ed. Godwin, London.
- Timsina, M.P., Martin, G.P., Marriott, C., Ganderton, D., Yianneskis, M., 1994. Drug delivery to the respiratory tract using dry powder inhalers. *Int. J. Pharm.* 101, 1–13.
- United States Pharmacopeia 24, 2000. United States Pharmacopeial Convention, Rockville, Maryland.
- Ward, G.H., Schultz, R.K., 1995. Process-induced crystallinity changes in albuterol sulfate and its effect of powder physical stability. *Pharm. Res.* 12, 773–779.
- Zhou, D., Zhang, G.G.Z., Grant, D.J.W., Schmitt, E.A., 2002. Physical stability of amorphous pharmaceuticals: importance of configurational thermodynamic quantities and molecular mobility. *J. Pharm. Sci.* 91, 1863–1872.



---

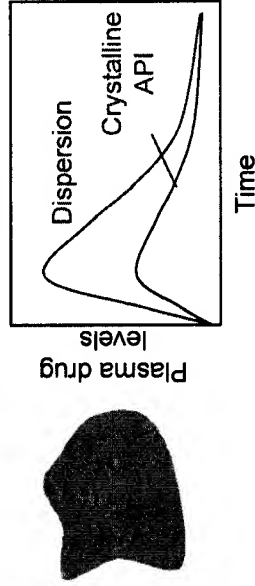
# Amorphous Solid Dispersions

---

Leah Appel Ph.D.  
Green Ridge Consulting

# Approach to Development of Amorphous Solid Dispersions

## Target product attributes



+

## Process understanding

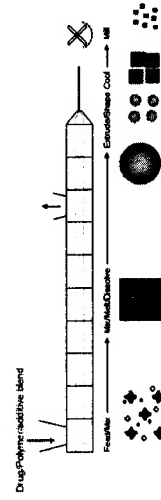
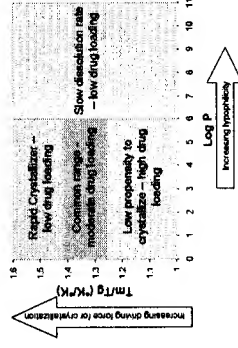


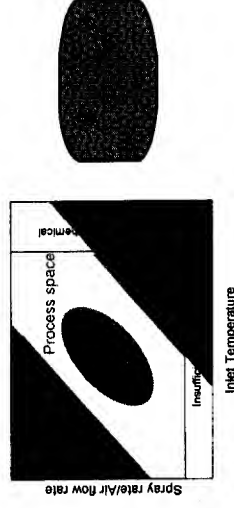
Exhibit G

## Product Development

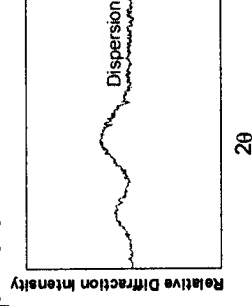
### Formulation development



### Process design



### Appropriate characterization





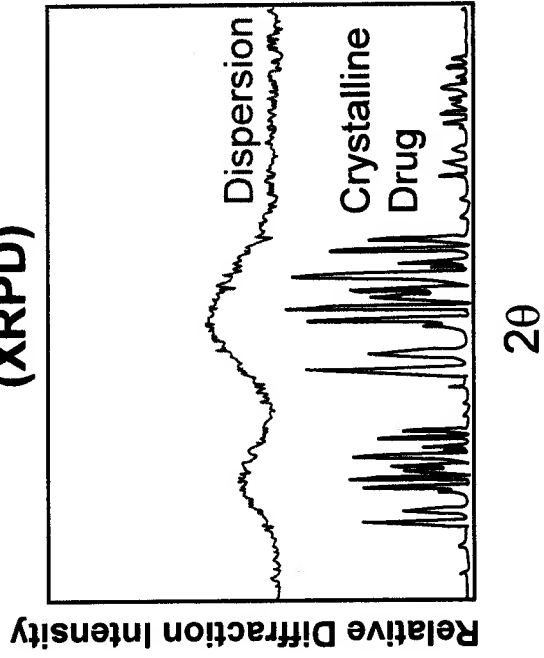
# Amorphous Solid Dispersions

Homogeneous molecular amorphous dispersion



- ~ Amorphous drug molecularly dispersed in polymer matrix
- Amorphous polymer matrix

## X-ray Powder Diffraction (XRPD)



## Differential Scanning Calorimetry (DSC)

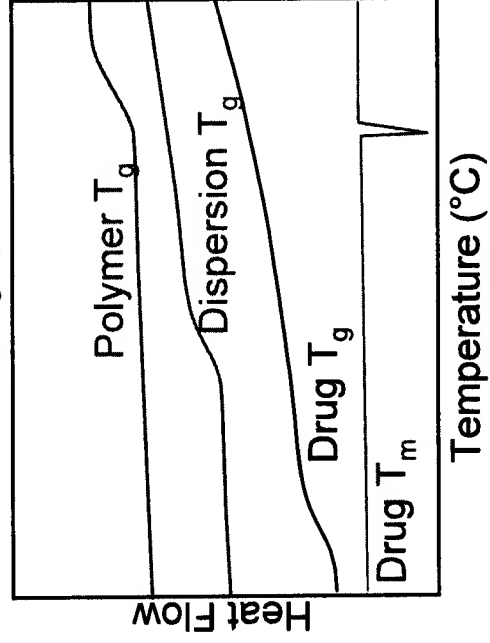


Exhibit G

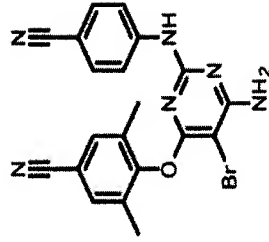
# Applications of Amorphous Solid Dispersions

---

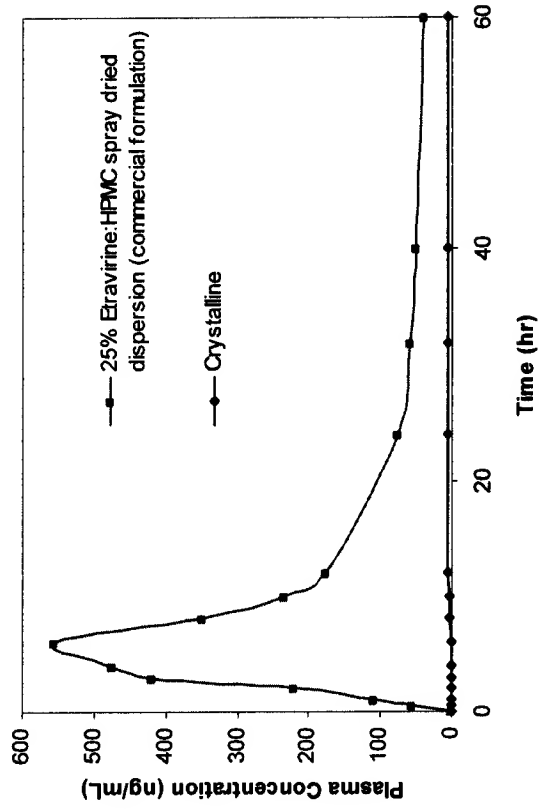
- Improve exposure (increase bioavailability, more rapid onset, decrease dose)
  - Support toxicology studies
  - Clinical tool
  - Commercial product
  
- Reduce variability
  - Decrease fed/fasted effect

# Example In Vivo Performance of Intelence, Etravirine Spray Dried Dispersion

Solubility	0.01mg/mL (aqueous)
log P	3.52 (calculated)
BCS Class	IV



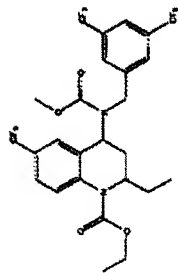
## In Vivo Performance



CCCC1=CN2C(=O)N=C2N1c3ccc(cc3)N4CCN(CC4)c5ccc(cc5)CO[C@H]6O[C@@H](C7=CC=C(C=C7)C(=O)N8C=CC=C8C9=CC=C(C=C9)C(=O)N10C=CC=C10)[C@H](C9=CC=C(C=C9)C(=O)N11C=CC=C11)[C@H]6O[illegible]

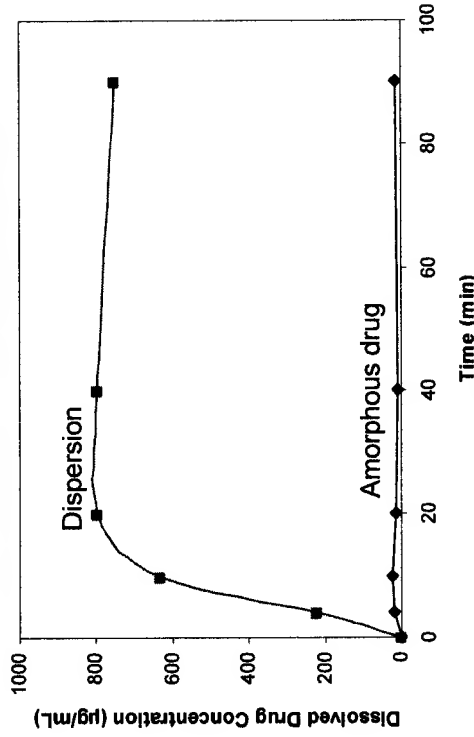
In vivo data: "Proof of Concept Study Factsheet." *Aptuit*. Web. 27 Jul. 2009. [http://www.aptnuit.com/en/Services/~/\\_media/9DF53184B5AE4A778299BC00EB446E21.ashx](http://www.aptnuit.com/en/Services/~/_media/9DF53184B5AE4A778299BC00EB446E21.ashx).

# Example In Vitro and In Vivo Performance of an Amorphous Dispersion of Torcetrapib

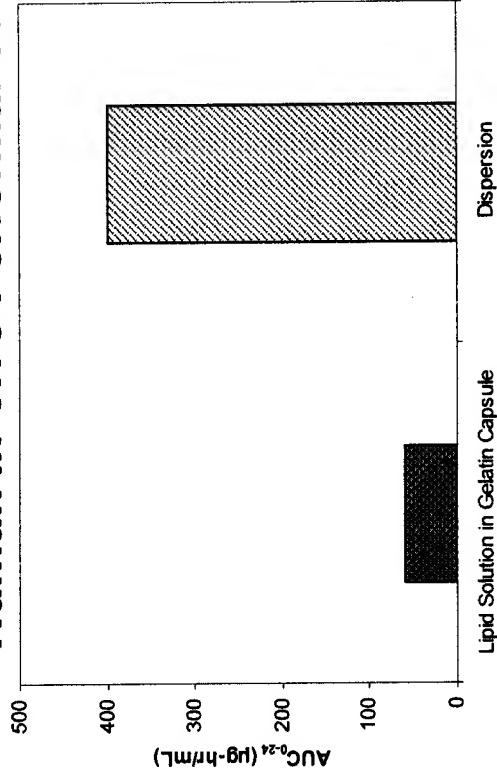


<b>Solubility</b>	<0.1 µg/mL (aqueous)
<b>log P</b>	6.7 (calculated)
<b>BCS Class</b>	II

## In Vitro Performance



## Human In Vivo Performance



## Canine In Vivo Performance

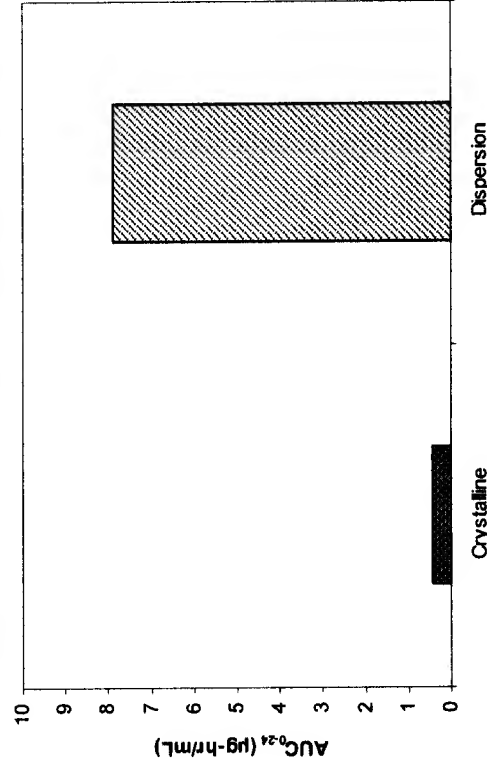


Exhibit G

# Precedented Amorphous Dispersions

Product	Compound (s)	BCS Class	Manufacturer	Dispersion Polymer	Dispersion Process	Max Dose (mgA)	Dosage Form
Kaletra	Lopinavir Ritonavir	IV	Abbott	PVP/VA	Melt extrusion	200/50	~ 1 g, tablet
Intelence	Etravirine	IV	Tibotec/Johnson & Johnson	HPMC	Spray drying	100	800 mg, tablet
Sporanox	Itraconazole	II	Janssen/ Ortho-McNeil	HPMC	Spray layering	100	460mg, capsules
Rezulin <sup>1</sup>	Troglitazone	II	Pfizer	PVP	Melt extrusion	400	Tablet
	Torcetrapib <sup>2,3</sup>	II	Pfizer	HPMCAS	Spray drying	60	< 1 g, tablet (combo tablet)

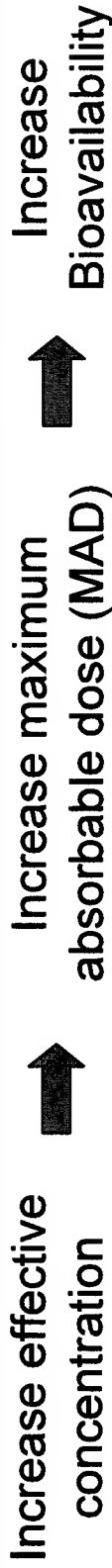
<sup>1</sup> Withdrawn from market in 2000 due to adverse drug events

<sup>2</sup> Ph III clinical trials halted in late 2006 due to adverse drug events

<sup>3</sup> Intended for dosing as a combination product with Atorvastatin

Exhibit G

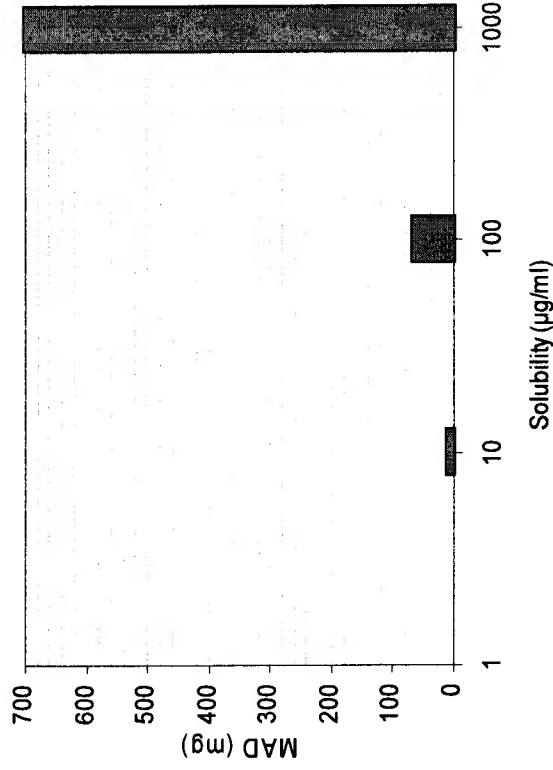
# Amorphous Solid Dispersions – How They Work



$$MAD = CK_a$$

C = concentration in region of absorption

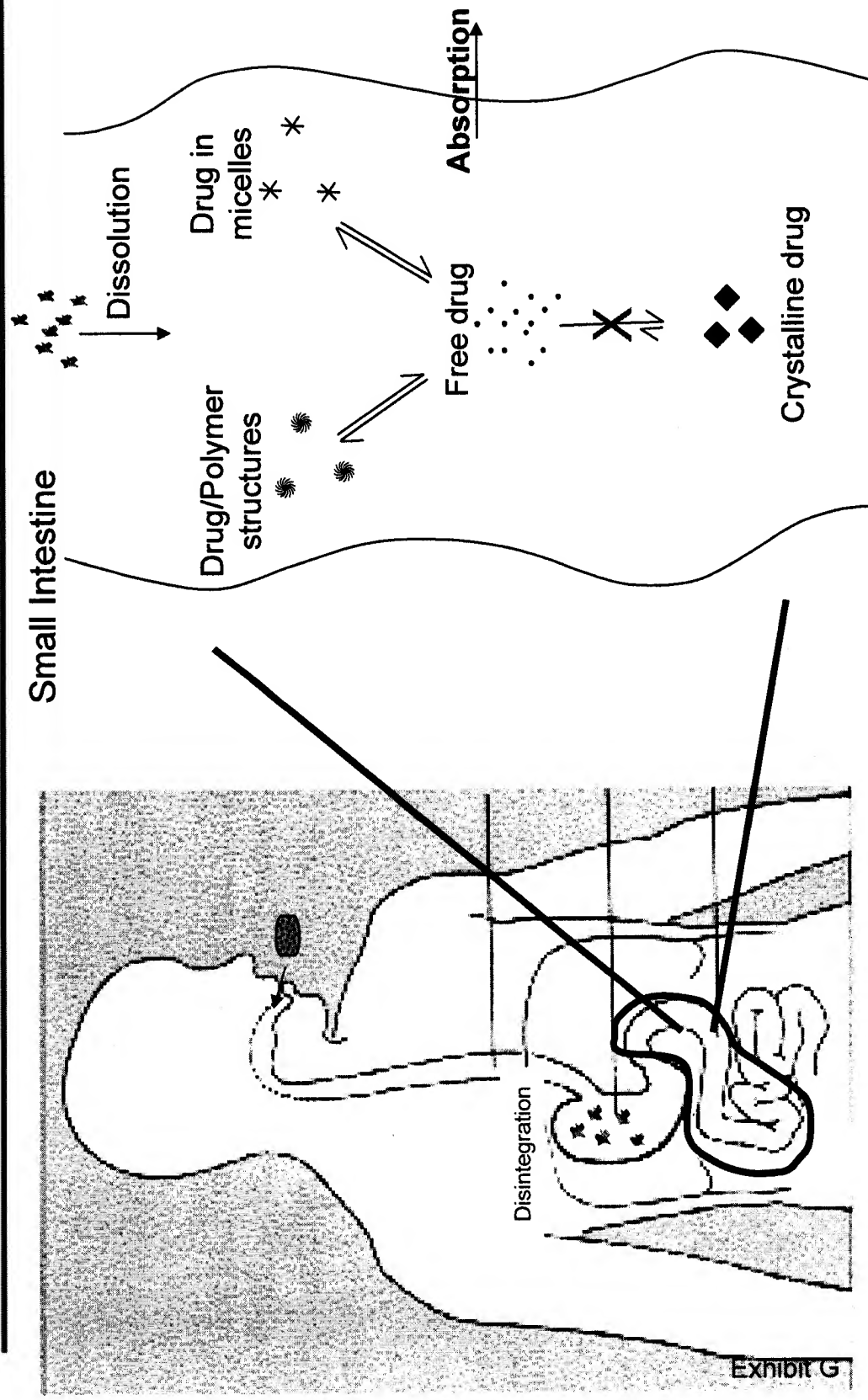
$K_a$  = absorption constant (function of permeability, surface area and residence time)



**10X increase in solubility  $\rightarrow$  10X increase in MAD**

Exhibit G

# Model for Absorption

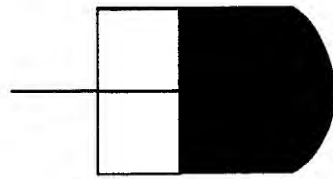




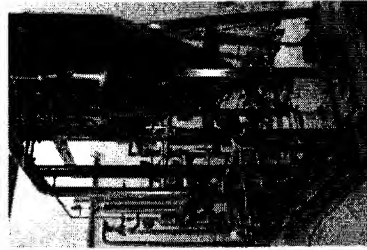
# Manufacture of Amorphous Solid Dispersions

- **Spray Drying**

- Solution of drug and polymer in a common solvent or solvent mixture



Spray solution

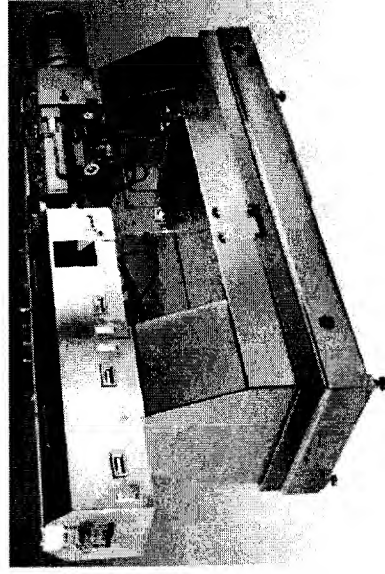
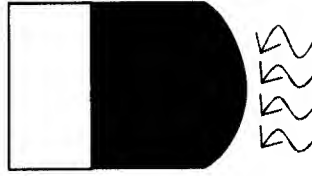


Courtesy of Anhydro

- **Hot-Melt Extrusion**

- Molten drug/dissolved drug and molten polymer

Melt



Reproduced with permission from  
American Leistritz Extruder Corporation

# Process Flow Chart Solid Dispersion Made by Spray Drying

**Prepare Solution                      Spray Dry                      Secondary Dry**

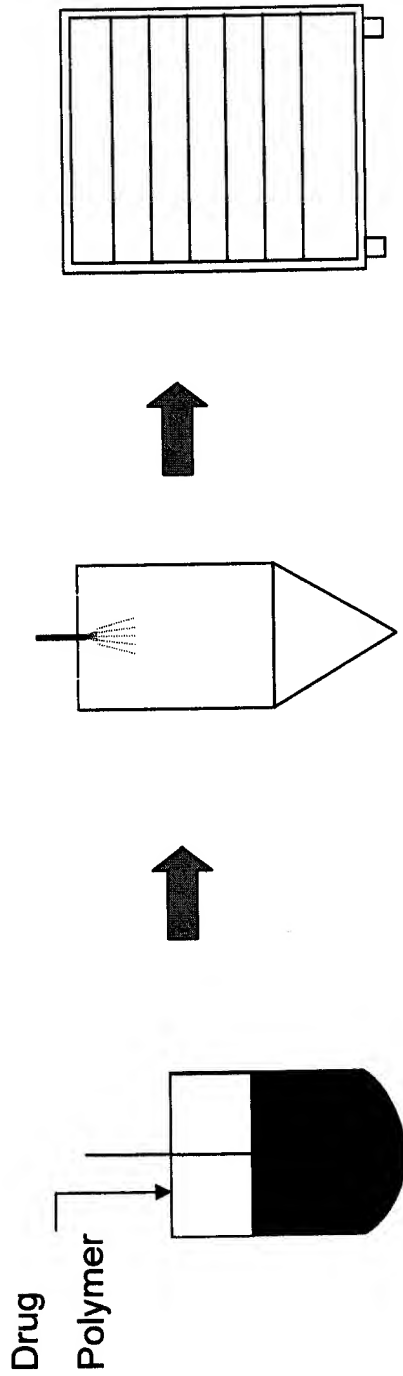
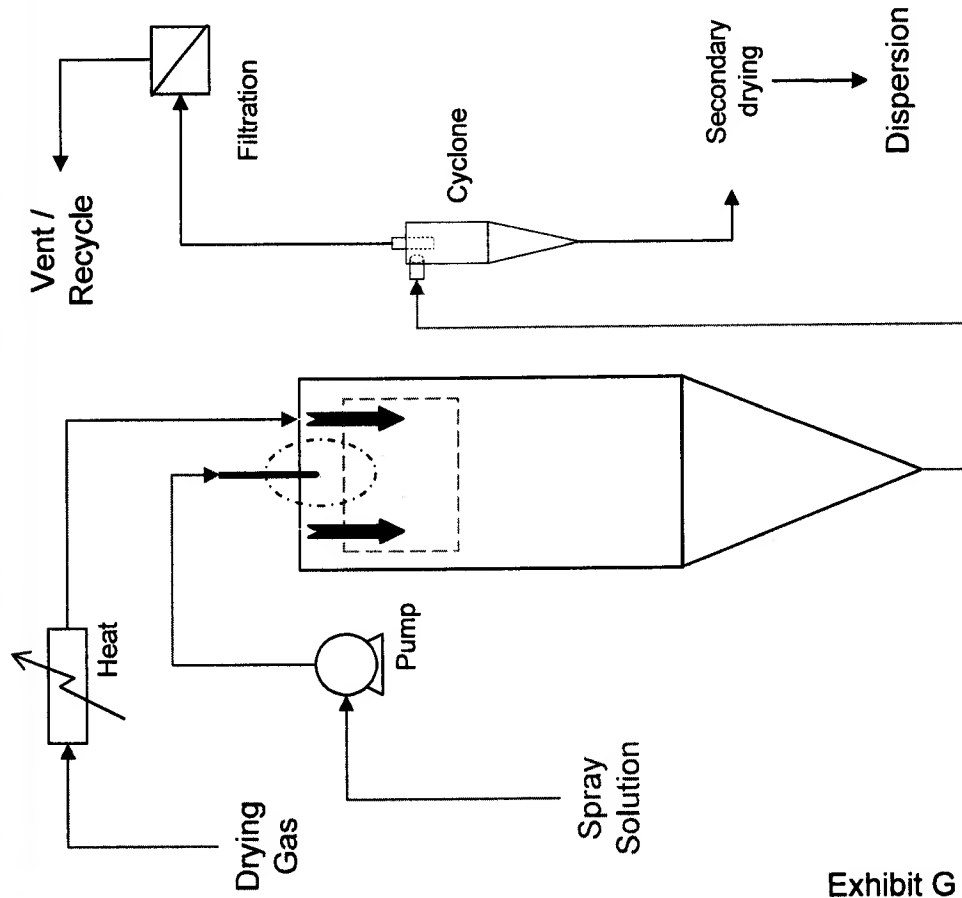
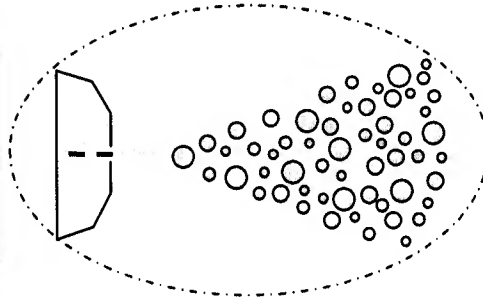


Exhibit G

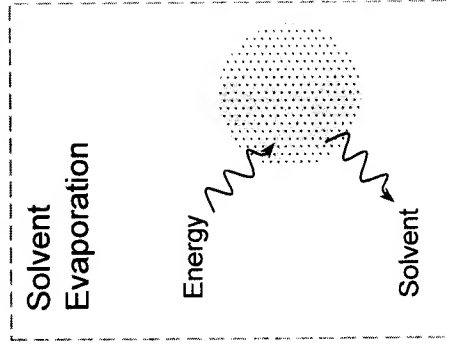
# Spray Drying Process Overview



## Atomization

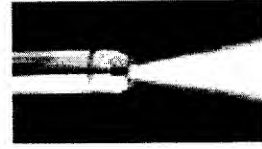


## Droplet Drying

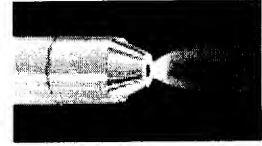


## Common Atomizers

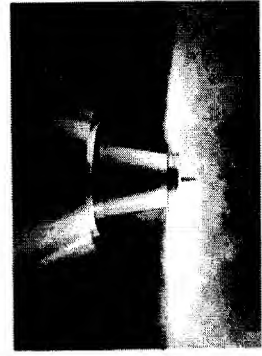
Two-Fluid



Pressure Swirl



Rotary



Reproduced with permission from GEA Niro, Inc.; [www.niroinc.com](http://www.niroinc.com)

Exhibit G

# Droplet Drying Overview

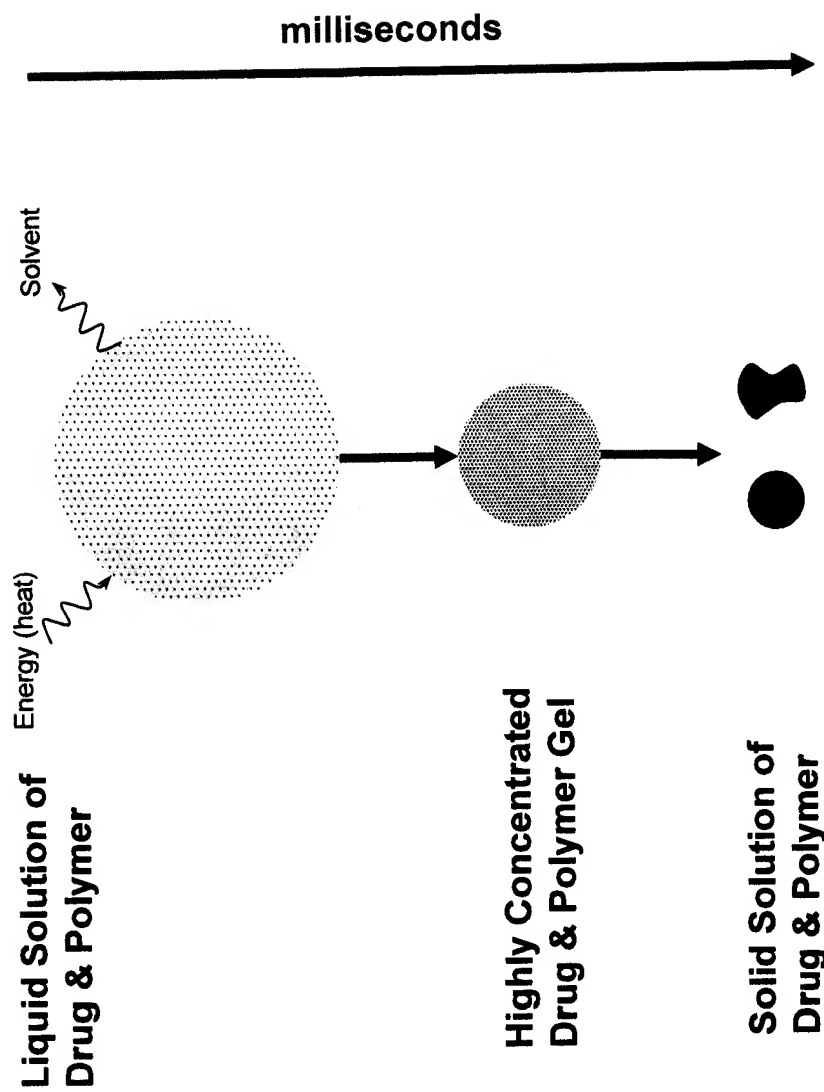


Exhibit G

# Factors Affecting Product Morphology Spray Drying

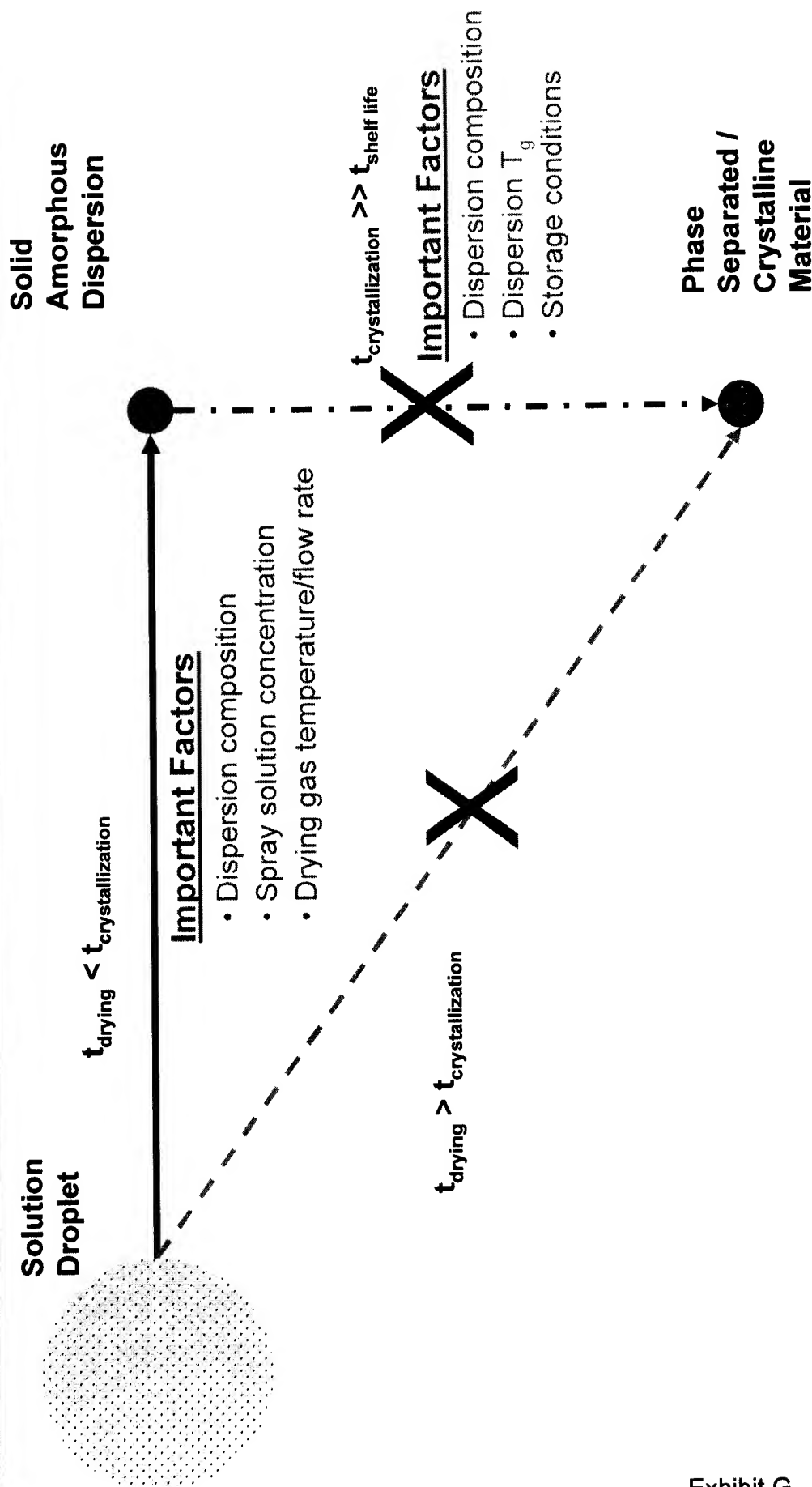


Exhibit G

# Process Space for Spray Drying

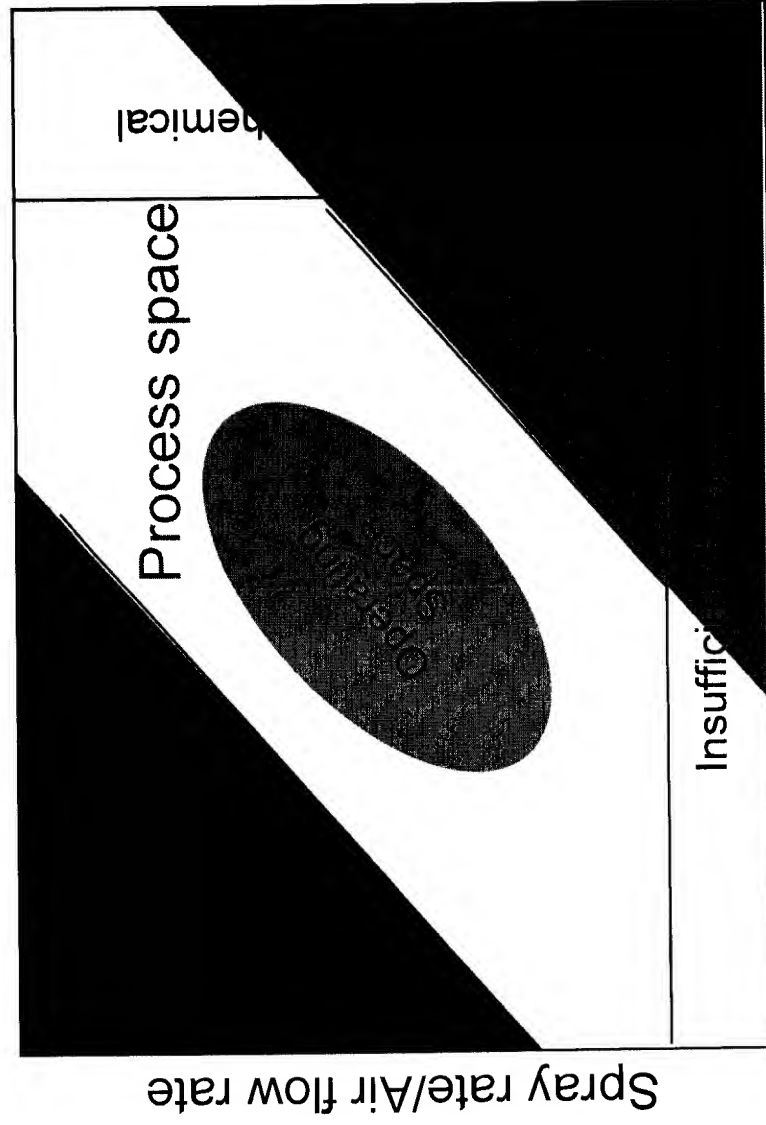
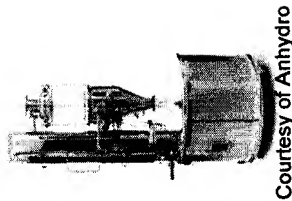


Exhibit G

# Scale-up Considerations Spray Drying

## Feasibility Phase I/II Phase III/ Commercial

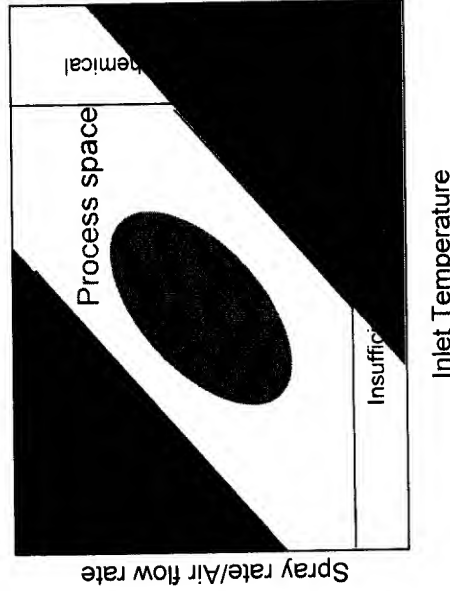
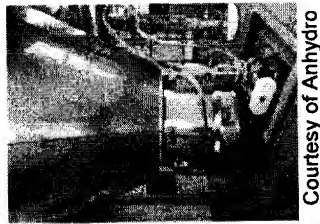


**Atomizer**  
(Droplet size)  
**Drying gas**  
(Mass transfer) single pass

pressure  
Recycle or  
single pass



pressure  
Recycle

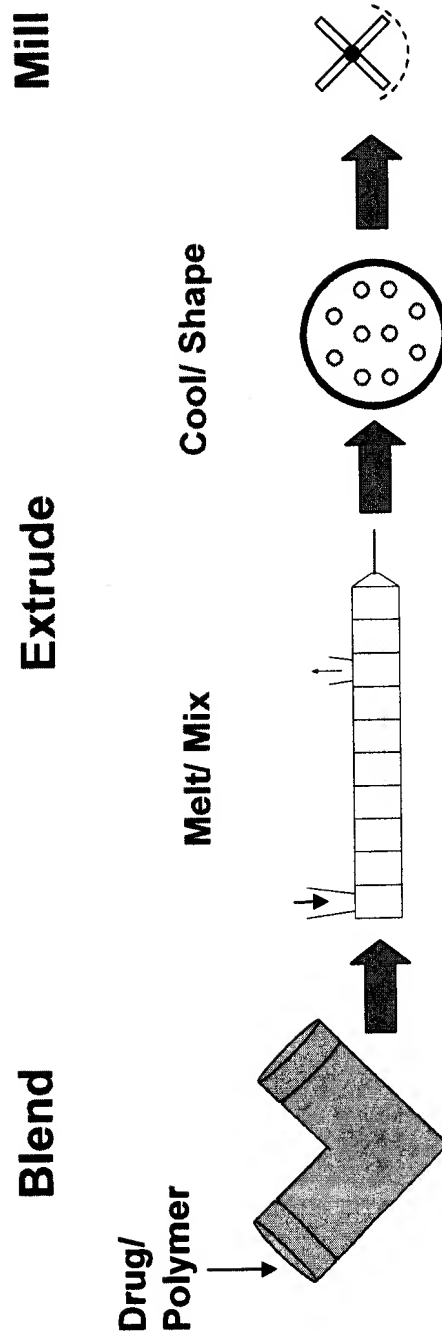


**Mass/Energy transfer**

Exhibit G

Slower drying  
Larger particles

# Process Flow Chart Solid Dispersion Made by Hot Melt Extrusion





# Physical Model for Extrusion of Amorphous Solid Dispersions

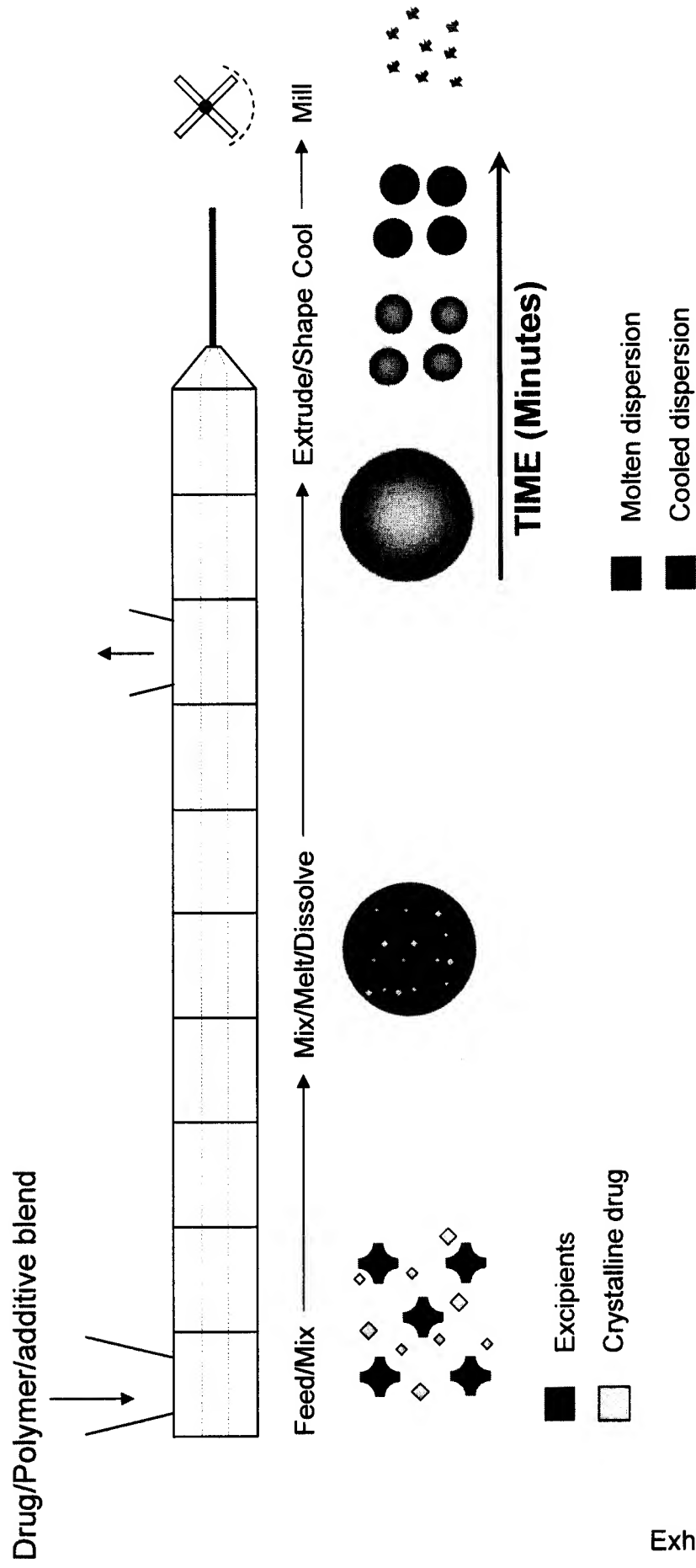


Exhibit G

# Factors Affecting Product Morphology

## Hot Melt Extrusion

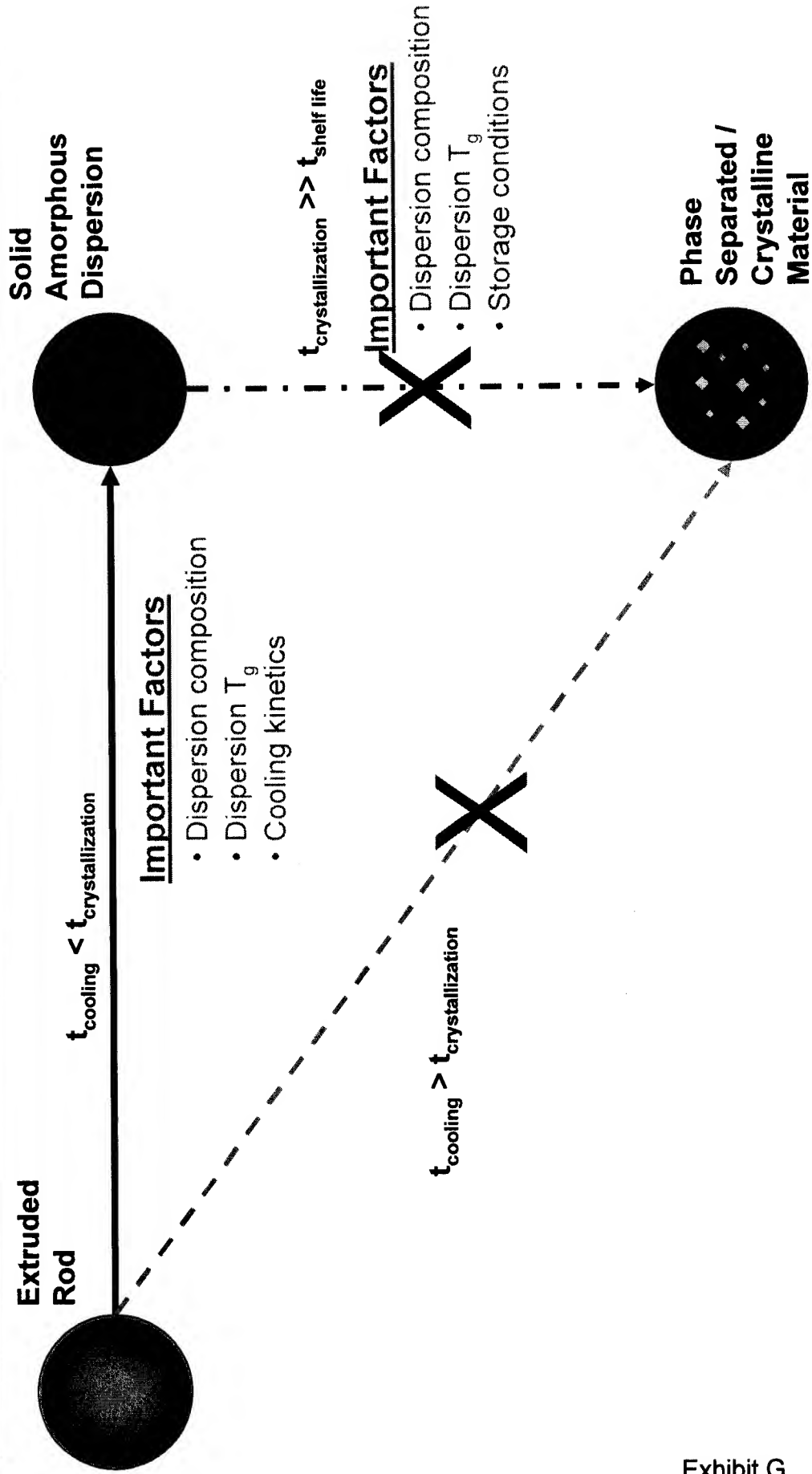
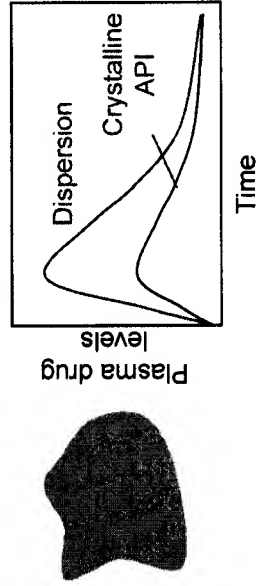


Exhibit G

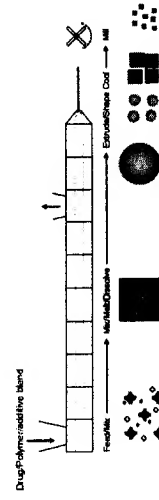
# Approach to Development of Amorphous Solid Dispersions

**Target product attributes**



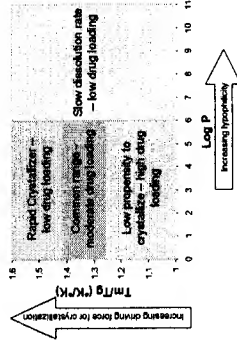
+

**Process understanding**

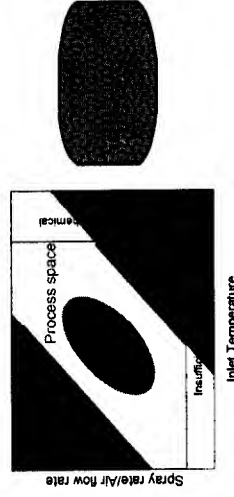


**Product Development**

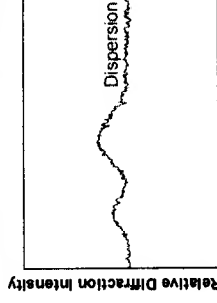
**Formulation development**



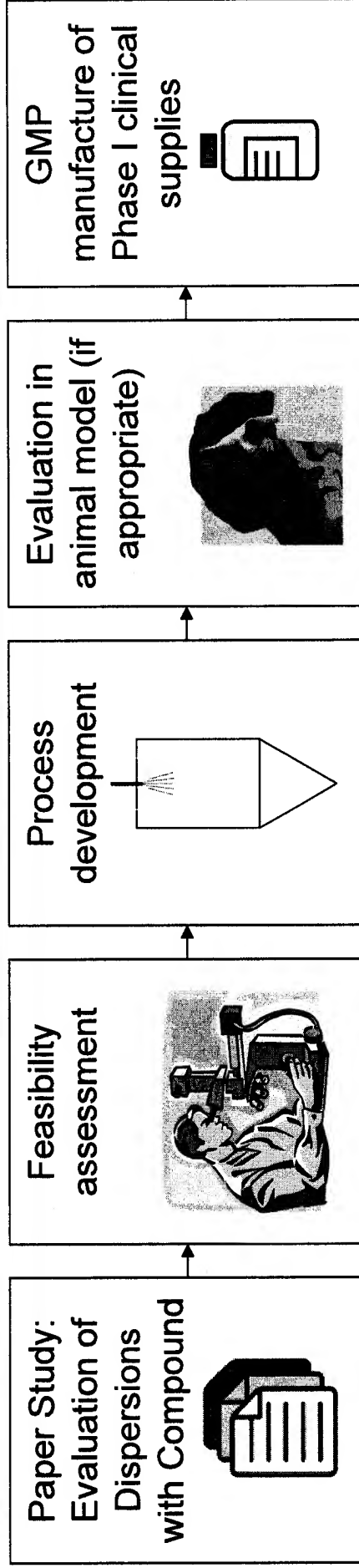
**Process design**



**Appropriate characterization**



# Steps in Initial Amorphous Solid Dispersion Development



## Output:

- Degree of difficulty
- Initial formulation/ process
- Small scale manufacture
- Performance
- Short term stability
- Longer term stability
- Dosage form development
- Rank order performance
- Ready for human evaluation

Exhibit G

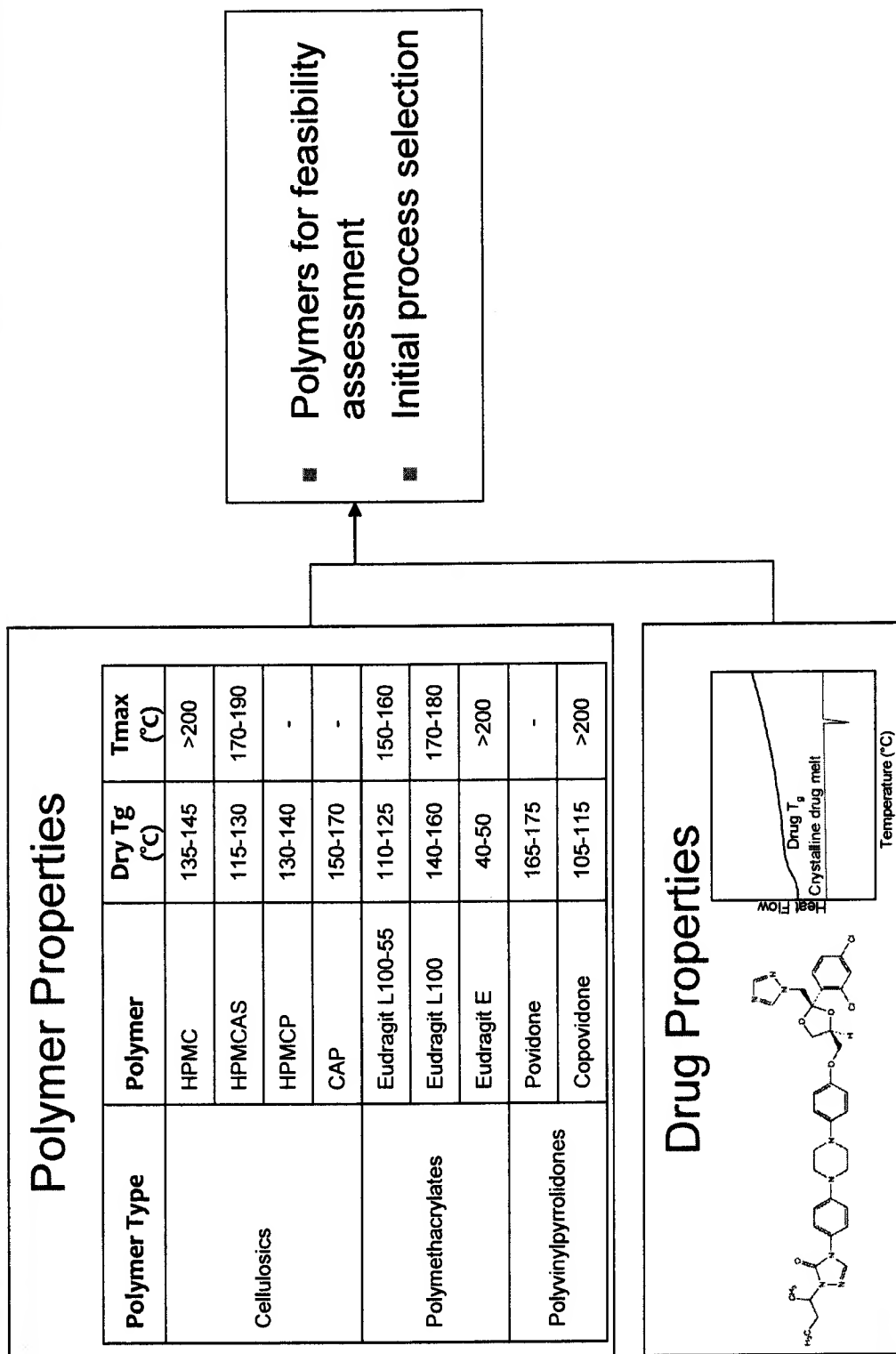


Exhibit G

# HPMCAS Amorphous Dispersion Map

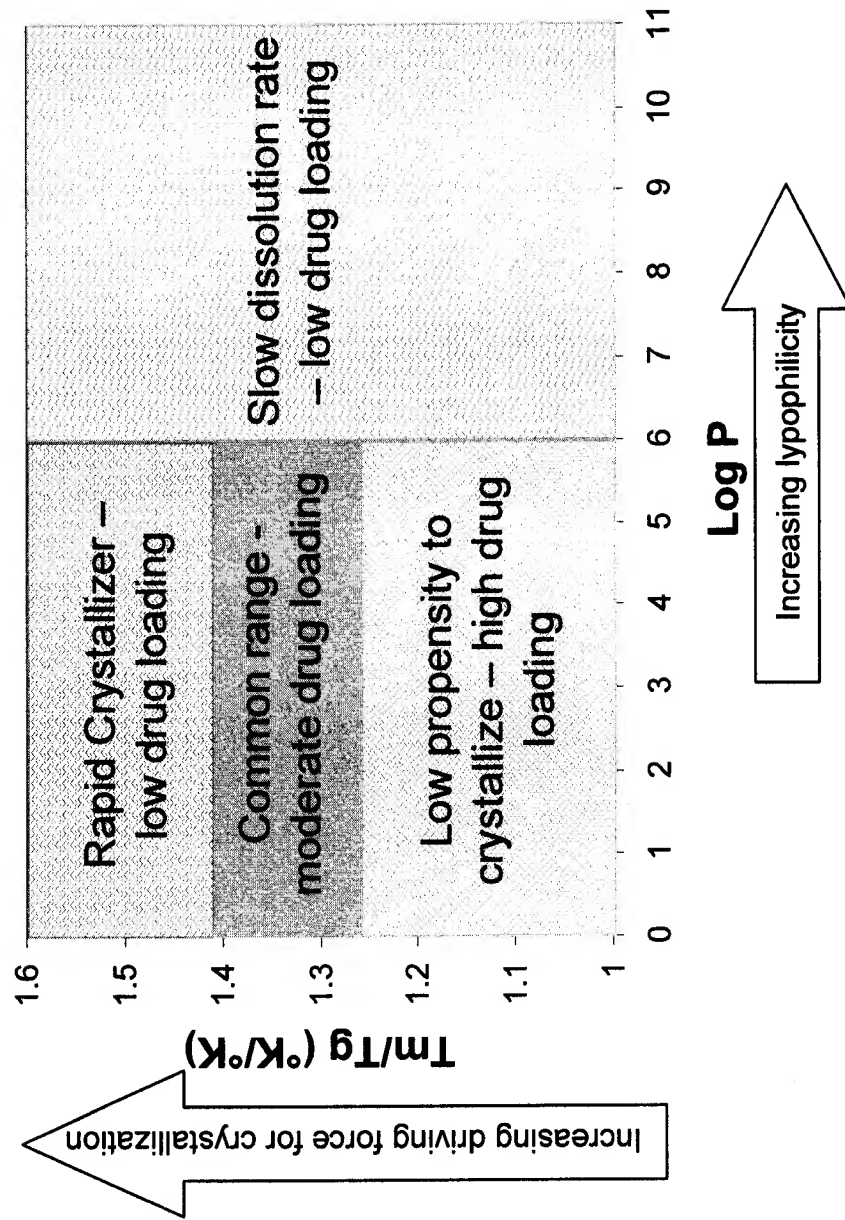
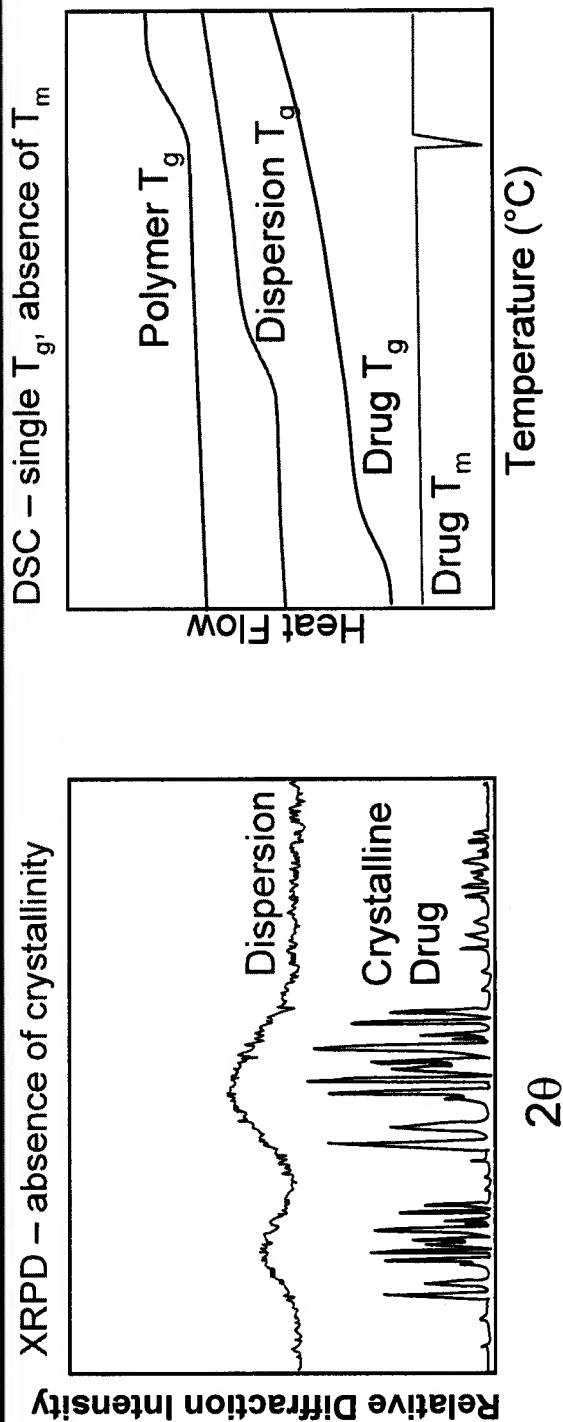


Exhibit G

Friesen, D.T., et. al. "Hydroxypropyl Methylcellulose Acetate Succinate-Based Spray-Dried Dispersions: An Overview". Molecular Pharmaceutics, 2008, 5 (6), 1003-1019.

# Solid State Characterization of Dispersions



SEM \* – absence of crystals



\*Reproduced with permission of ACS Publications. Friesen, D.T., et. al. "Hydroxypropyl Methylcellulose Acetate Succinate-Based Spray-Dried Dispersions: An Overview". Molecular Pharmaceutics, **2008**, 5 (6), 1003-1019.

- Non-sink dissolution testing in bio-relevant media
    - Degree of supersaturation
    - Sustainment of supersaturation
- } *Use to optimize formulations and rank-order lead selections*

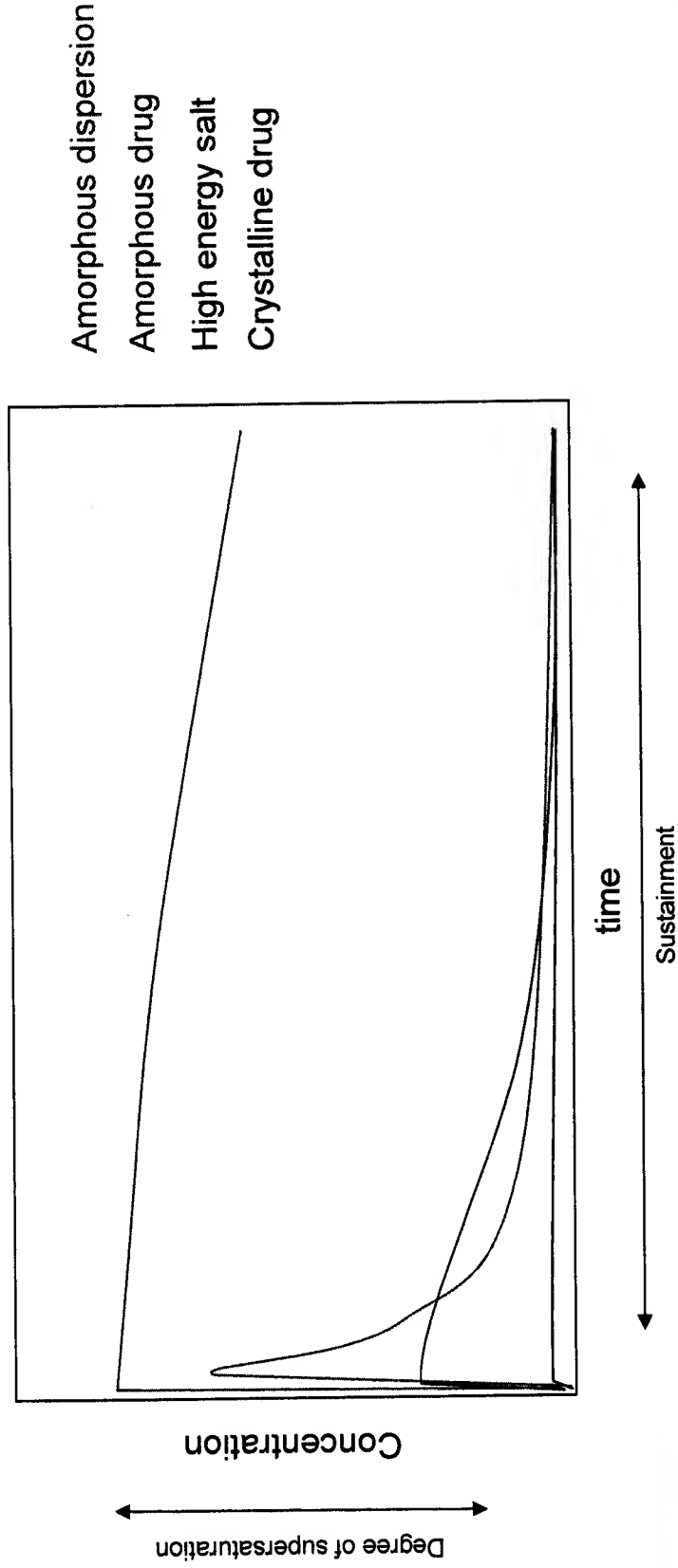
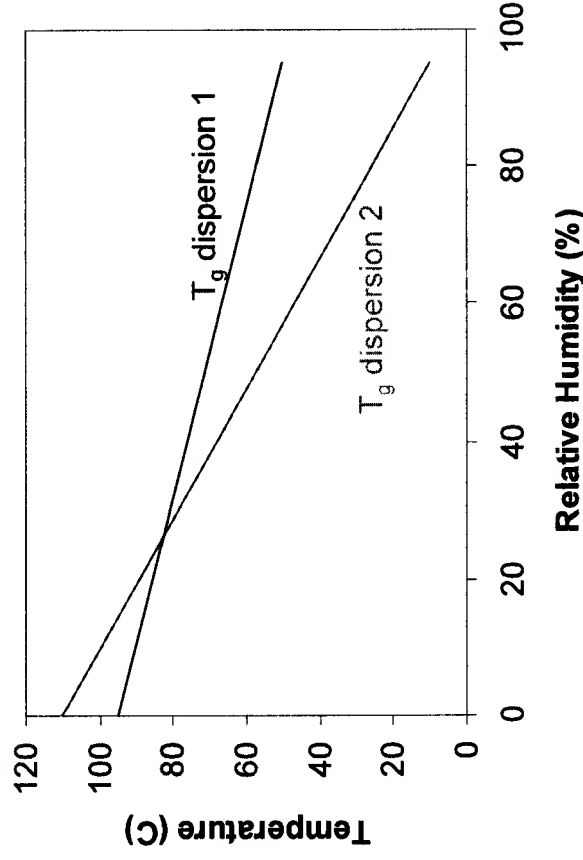


Exhibit G



# Initial Physical Stability Assessment of Amorphous Solid Dispersions



Guidance on:

- Formulation selection
- Packaging needs

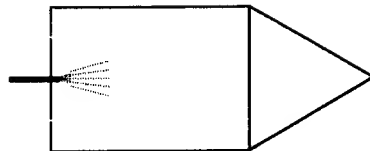
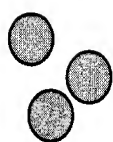


## Stability tests

- Scientific understanding
  - Use open conditions to understand effect of RH and temperature on physical stability
- Regulatory
  - Use packaged conditions to support clinical expiry

# Amorphous Solid Dispersions and Solid Dosage Form Development

**Dispersion**      **Final Dosage Form**



or

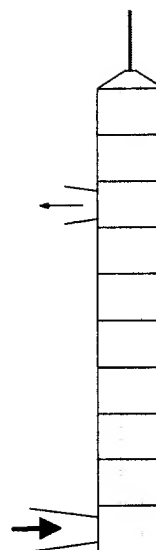
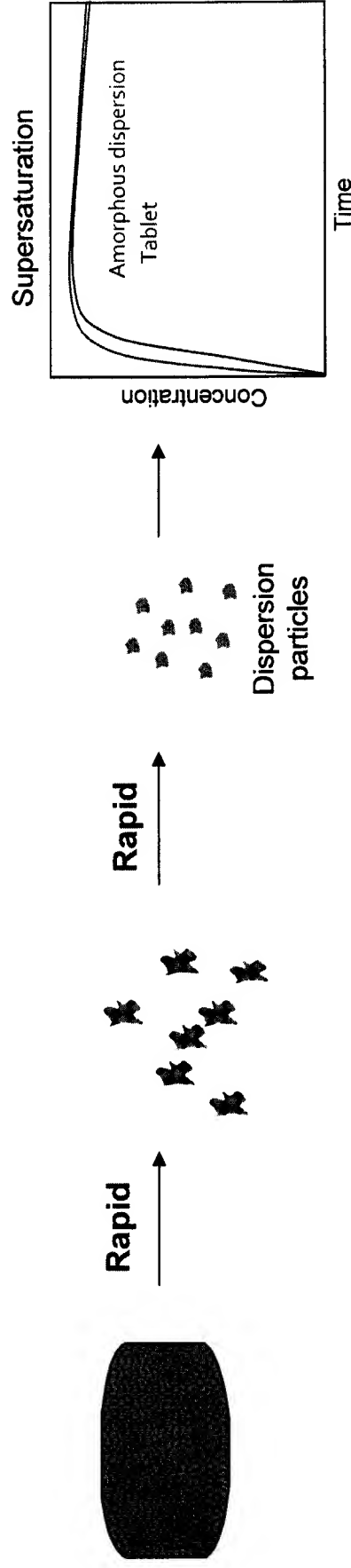


Exhibit G

- ❑ Rapid disintegration
- ❑ Maintain dispersion performance from dosage form



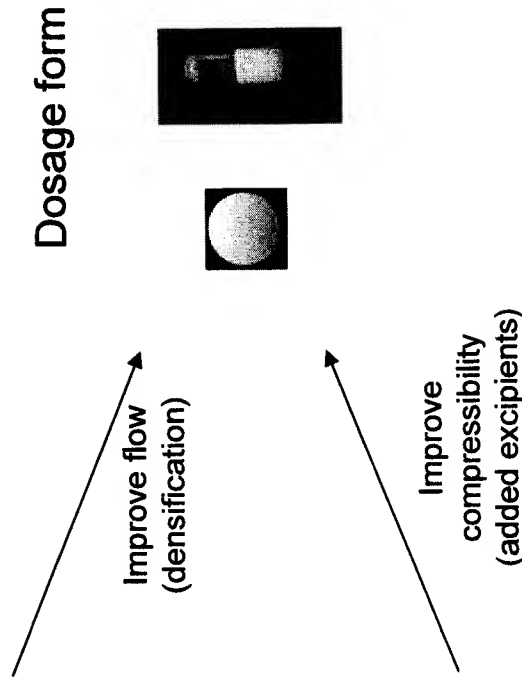
# Spray Dried Dispersion Solid Dosage Form Development

## Spray Dried Dispersion Powder

- Low density, fluffy powder
- ~20-100µm

## Hot Melt Extruded Dispersion Particles

- Hard, dense particles
- ~0.5-2mm



### Common dispersion issues:

- Moisture/solvent sensitive
- May gel when hydrated
- Polymer properties can dominate dispersion properties

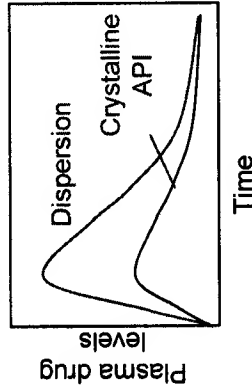
### Common dosage form issues:

- Rapid disintegration/dissolution
- Drug loading/maximum dose
- Maintaining physical stability of dispersion
- Granulation
- Coating

# Summary

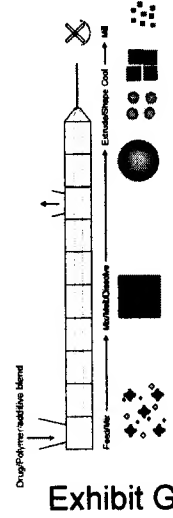
## Product Development Scale-up/ Transfer

Target product  
attributes

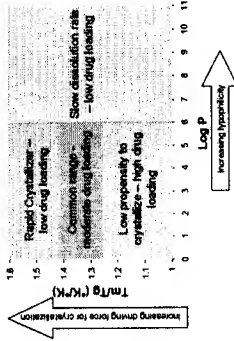


+

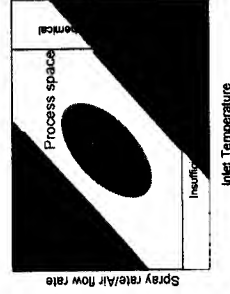
Process  
understanding



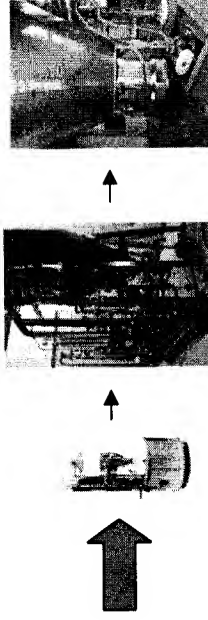
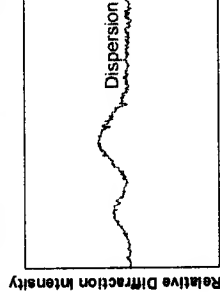
Formulation development



Process design



Appropriate characterization



Courtesy of Anhydro

## HOVIONE EXPANDS ITS PARTICLE DESIGN TECHNOLOGIES WITH THE LATEST cGMP SPRAY DRYER FACILITY

By Jorge Pastilha, Director of Logistics & Control and  
Filipe Gaspar, PhD, Process Engineer  
Hovione, SA

The interface point that lies between the making of an API and its formulation into a pill, an injectable or inhaled drug is an area fraught with complexity – API particle size and crystal form have a direct impact on the performance of a drug, and yet in the list of the top contractors for custom synthesis there appears to be surprisingly few that claim to have any expertise in this area.

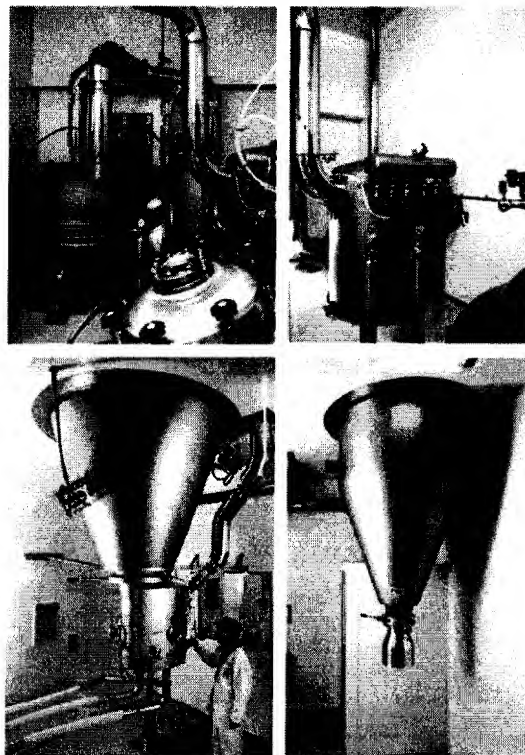
One explanation for this state of affairs may be the tradition that large multinationals have to keep the last step of the API in-house. The one manufacturing strategy that all pharmaceutical multinational appear to have in common is the locating of the final stages of the API synthesis in Puerto Rico, Ireland and now Singapore. This fiscal focus has caused most contract manufacturers of APIs to remain focused in supplying advanced, cGMP compliant, intermediates to the Large Pharma. They have therefore had little opportunity to develop know-how around the physical attributes of the final API.

The emergence of Small Pharma has inverted this trend. Those offering Custom Synthesis are now expected to deliver everything related to the API – this includes analytical chemistry, synthesis route innovation coordinated with raw-material sourcing, process development, regulatory filings and manufacturing in an environment characterised by compliance and service orientation – included, but often neglected, is the ability to speak the language of the next link in the chain: the formulator. Chemists and engineers do not, by training, recognize the challenges that formulators face in taking their API forward and turning it into a successful drug. Hovione has been making nothing but final APIs for over 40 years as such we have been acutely sensitive to the technical requirements of those that use the APIs we make.

In line with the latest developments on spray drying technologies and with the increasing demand for highly defined particles properties in the pharmaceutical industry, Hovione has installed and commissioned, at its manufacturing plant in Portugal, a state-of-the-art spray-drying unit able to operate under the most stringent cGMP conditions. The multipurpose unit is fit to deliver injectable grade APIs and is configured to be "cleaned-in-place", discharging into a classified clean-room.

### Benefits of Spray Drying in Pharmaceutical Fine Chemicals

The service of an API manufacturer not only involves the development of the chemical process and the supply of high quality API, when and where required, but also paying close attention to those physical parameters which make up the necessary requisites for a successful



Schematic composition of cGMP Spray Dryer installation

formulation. Chemical skills must be complemented by a pharmaceutical culture. For a successful custom synthesis partnership it is imperative that the API contractor be both cognizant of the importance of having the product with the correct particle properties, and be able to develop a process that delivers it consistently. It is well known that properties such as particle size distribution and morphology affect important parameters such as bioavailability, dose uniformity and formulation. This is key in many galenic forms; in the field of inhalation for instance it is absolutely critical; it can also be the source of many last-minute surprises and frustrations until the matter is well controlled.

API's are typically produced by extraction or chemical syntheses and most often isolated through a multiple-step process comprising controlled crystallization, solid-liquid separation and drying. A post-drying step such as micronization is frequently needed to adjust particle properties such as size distribution and bulk density. Some pharmaceutical compounds are particularly difficult to micronize by conventional grinding or jet milling. For example, materials that have low melting

point or that are waxy can smear or form amorphous (and size unstable) particles.

Spray drying is presently one of the most exciting technology for the pharmaceutical industry, being an ideal process where the end-product must comply to precise quality standards regarding particle size distribution, residual moisture content, bulk density and morphology. Already widely used for the manufacture of many consumer and industrial products such as instant food, laundry detergents, ceramics and agrochemicals, the growth in pharmaceutical spray drying was driven by a number of advantages over conventional multiple-step processes and competing particle reduction technologies. It allows not only to replace, in many processes, all the complex, time-consuming and yield-reducing isolation steps but also to produce API's with tailor-made particle properties.

Another advantage of spray drying is the remarkable versatility of the technology, evident when analyzing the multiple applications and the wide range of products that can be obtained. From very fine particles for pulmonary delivery to big agglomerated powders for oral dosages, from amorphous to crystalline products and the potential for one-step formulations, spray drying offers multiple opportunities that no other single drying technology can claim.

#### From very fine particles to agglomerates

Spray drying involves the continuous atomization of the feed solution into a hot drying gas, most commonly air or nitrogen. The fine droplets resulting for the atomization of the feed solution are immediately exposed to the drying gas leading to supersaturation and resulting in the formation of ultra fine particles, typically below 5 micron and with a tight particle size distribution, which are collected via a cyclone (see Fig. 1). These highly defined particles have promoted spray drying as a method of choice for the production of powders for inhalation.

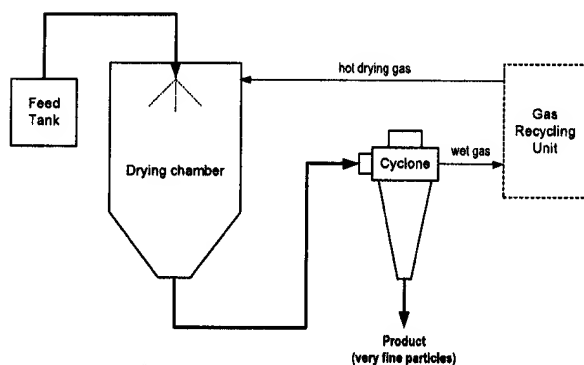


Fig. 1 – Very fine particles from spray drying

Moreover, technological developments in the construction of spray dryers have also stimulated the application of this technology in the production of agglomerates for the pharmaceutical industry. In the early nineties spray dryer with integrated fluid bed became the most important spray drying concept in the food and chemical industries for producing agglomerated powders. Several large-scale plants were commissioned for the production of milk powder and

soluble coffee and the concept was extended to the pharmaceutical fine chemical industries namely in the preparation of Captisol®, a leading proprietary cyclodextrin that Pfizer uses in the formulation of its compounds Geodon and Vfend. The agglomerated powders are produced by re-introduction of the very fine particles into the drying chamber (see Fig. 2). The dry fine particles in contact with wet particles form agglomerates with enhanced handling properties. These dust-free agglomerates are free flowing powders, which are far easier to dissolve in their final application avoiding the formation of suspended lumps of product.

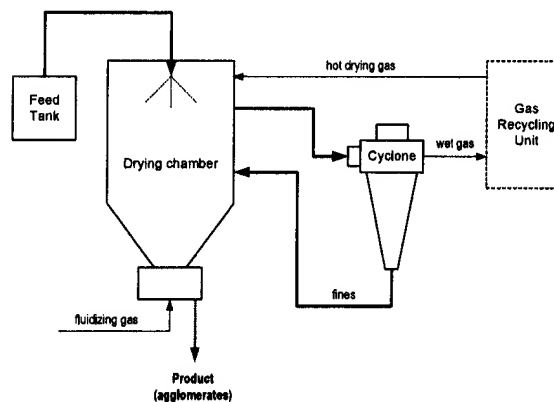


Fig. 2 – Agglomerates from a Fluidized Spray Drying

#### From amorphous to crystalline products

When starting from a product solution, spray drying is known to produce predominately amorphous material due to the almost instantaneous transition between liquid and solid phases. This is often desirable as it may be used to increase the bioavailability of the resulting product. However, spray drying can also be used to obtain crystalline products with defined sizes and controlled residual solvent contents. To achieve such goal, the product is fed in a crystalline suspension, instead of a solution, to the drying chamber. Feeding the crystals already in the right form, allows spray drying to fine tune crystal size distribution and final content of residual solvents. In between these two extremes it is also possible to manipulate the degree of crystallinity of the product, enhancing control over physiochemical properties and functionality of the final product.

#### Ideally suited for heat sensitive products

Contrary to a general misconception, spray drying is a very gentle drying technology when dealing with thermal labile compounds. The shielding effect of the solvent during drying protects the product contained in the core of the fine droplets from the bulk temperature in the drying chamber, typically between 70 and 150°C. In addition, exposure time is extremely low, usually a few seconds, minimizing the heat "shock" and the potential degradation of the product molecules. The gentleness of the drying process together with the ability to provide highly defined particles with tunable properties and the lower processing costs makes spray drying a true and economical alternative to freeze drying when handling heat sensitive products.

#### Formulation in a one-step process

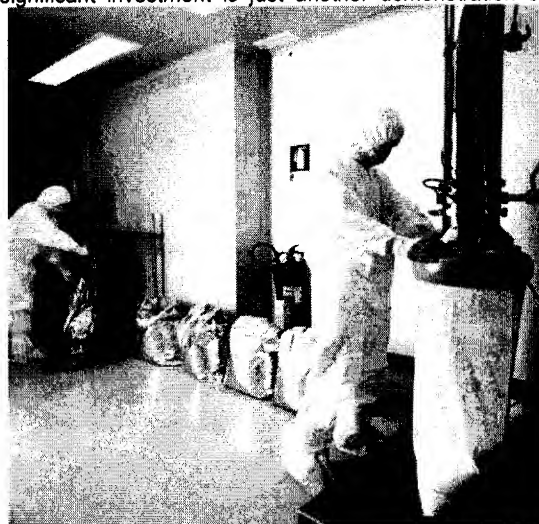
Several other applications of spray drying have recently been proposed within the pharmaceutical industry. The ability to co-spray drying different materials, arising from the extremely short time-scale of the drying process allows, for example, for homogeneous co-precipitation and continuous encapsulation techniques. This opens up a spectrum of opportunities for the creation of improved formulated products.

#### **cGMP spray-drying Multipurpose and across a range of scales**

This fully automated unit operates under the most stringent cGMP conditions and can be configured both as a conventional spray dryer for the production of very fine particles (< 5 – 10 micron) and as a fluidized spray dryer when producing agglomerated, free-flowing dustless materials (100 – 400 micron). Supplied and designed by Niro A/S to the most advanced specifications, this multipurpose unit is capable of evaporating 35 to 90 Kg of water per hour and is equipped with two atomizer systems (a pressure nozzle and co-current two-fluid nozzle). The facility allows producing continuously dry solids in either powder, granulating or agglomerating form from liquid feedstocks such as solutions, emulsions and pumpable suspensions; the system meets the most stringent explosion-proof requirements and can therefore spray-dry out of most organic solvents in a safe and compliant environment. When using nitrogen as the drying gas, the unit operates in a closed cycle thus enhancing its safety and economical production aspects.

Hovione's services in process chemistry and manufacturing span the complete range of scales – from lab to pilot to commercial scale, and spray drying can be

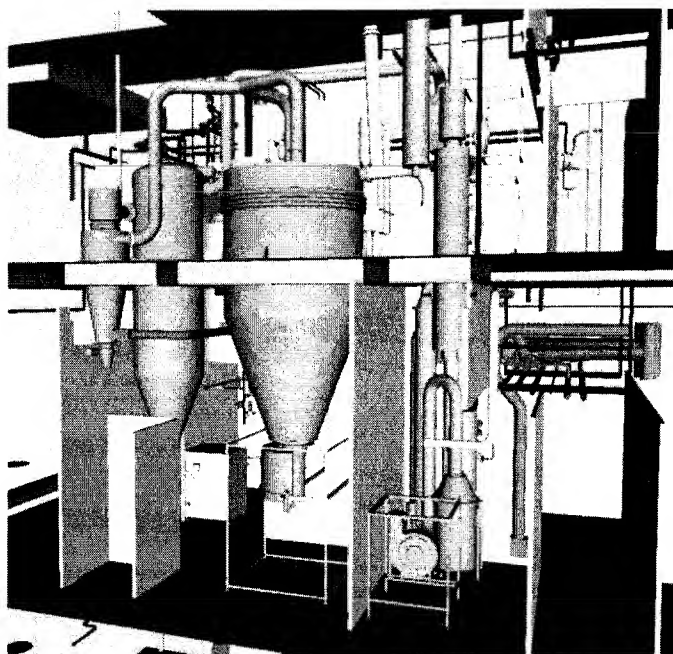
carried out across all of them at our sites. Although this article has focused on spray drying, for us this recent significant investment is just another demonstration of



**Discharge of final product into a classified clean-room**

our commitment to finding solutions for our customers' API needs. To be a specialist in APIs means we need to be generalists able to address any chemistry and engineering challenge, to provide customers with immediate access to every tool, and to speak not just their language but also that of regulators, patent lawyers and their contract formulators.

For more information visit Hovione's site [www.hovione.com](http://www.hovione.com); Captisol is a registered trademark of CyDex [www.cydexinc.com](http://www.cydexinc.com), Vfend and Geodon are registered trademarks of Pfizer Inc.



**Spray dryer installation – from spray dryer to fluidized spray dryer in one multipurpose unit**